DOCTOR OF PHILOSOPHY In the field of Chimie organique Application of the Radical Chemistry of Xanthates to the Synthesis of Cyclic or Acyclic Amines

Songzhe Han

THESIS

Submitted for the award of the degree of

DOCTOR OF PHILOSOPHY

In the field of

Organic Chemistry

By

Songzhe HAN

Application of the Radical Chemistry of Xanthates to the Synthesis of Cyclic or Acyclic Amines

Presented on September 29, 2014 to a committee composed of:

Prof. Erwan Poupon	Referee
Dr. Boris Vauzeilles	Referee
Dr. Raphaël Dumeunier	Examiner
Prof. Samir Z. Zard	Director of thesis
Prof. Isabelle Gillaizeau	President

Acknowledgement

I am using this opportunity to express my gratitude to everyone who supported me throughout my three years' PhD study. I am thankful for their aspiring guidance, invaluably constructive criticism and friendly advice during the project work. I am sincerely grateful to them for sharing their truthful and illuminating views on a number of issues related to the projects.

I express my warm thanks to Prof. Samir Z. Zard who is my supervisor and not only teaches me something in doing research but also something for a better life. Till now I still remember some words from him like "Stupid guy learn from their own mistakes and smart guy learn from others' mistakes" which are something I will remember in the rest of my life. And it is a great honor to work as his PhD student during the three years.

I would also like to thank Dr Béatrice Sire. She is a very kind and generous lady. Whenever people meet some problems in the lab, she will always find time to help you first. And I especially thank her for encouraging me to learn French and help me improve my French.

My special thanks to Brigitte, Lédia, Dr. Yvan Six and Dr. Fabien

Gagosz for their all kinds of help and meaningful advices during the three years.

I would like to thank all the other students who share some experiences with me together during my three years' PhD study.

Finally, I would like to show my deep gratitude to my family: my parents and my wife for their all kinds of supports in my life without whom I couldn't have such achievements.

CONTENTS

Abbreviations

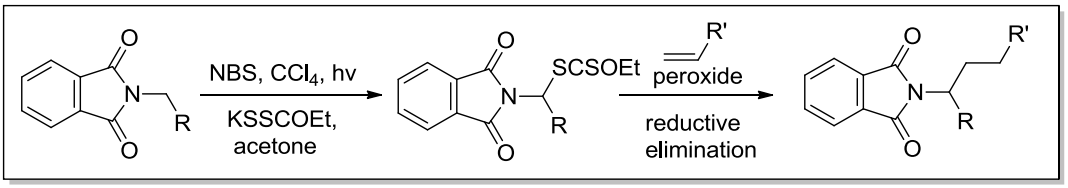
Ac	**acetyl**
AIBN	**2,2'-azo-*bis*-isobutyronitrile**
Ar	**aryl**
Bn	**benzyl**
Boc	***tert*-butoxycarbonyl**
DBU	**1,8-Diazabicyclo[5.4.0]undec-7-ene**
DCE	**1,2-dichloroethane**
DCM	**dichloroethane**
DIPEA	***N,N*-Diisopropylethylamine**
DLP	**dilauroyl peroxide**
DMAP	**4-dimethylaminopyridine**
DMF	***N,N*-dimethylformamide**
DTBP	**di-*tert*-butyl peroxide**
EP	**petroleum ether**
Et	**ethyl**
i-Pr	**isopropyl**
LDA	**lithium diisopropylamide**
***m*-CPBA**	***meta*-chloroperoxybenzoic acid**
Me	**methyl**
Ms	**mesyl**
Ph	**phenyl**
PhCl	**chlorobenzene**
Phth	**phthalimide**
PTSA	***p*-toluenesulfonic acid**
Piv	**pivalate**
***t*-Bu**	***tert*-butyl**
TEA	**triethylamine**

TFA	**trifluoroacetic acid**
THF	**tetrahydrofuran**
TMS	**trimethylsilyl**
Ts	**tosyl**
Xa	***O*-ethyl xanthate**
cat.	**catalytic quantity**
°C	**degree Celsius**
equiv.	**equivalents**
Δ	**heating**
Hz	**hertz**
h	**hour**
IR	**infrared**
min	**minute**
M	**mole per litre**
NMR	**nuclear magnetic resonance**
ppm	**parts per million**
hv	**photochemical irradiation**
TLC	**thin layer chromatography**

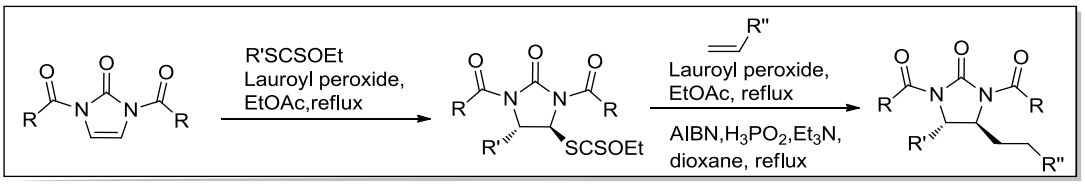
Avant-propos

Avant-propos

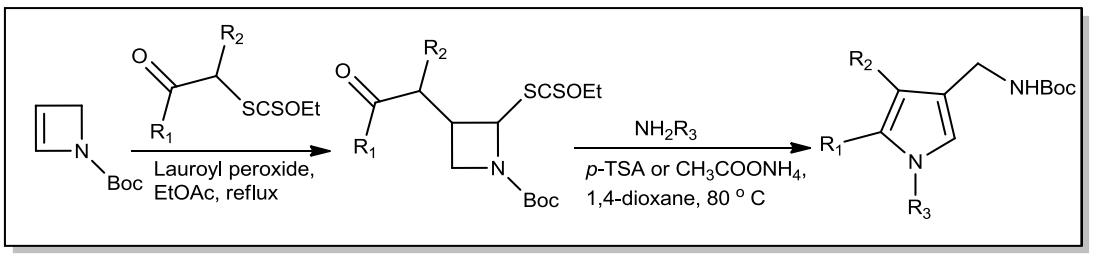
Le travail de thèse de mené par monsieur Songzhe HAN comporte trois parties. La première concerne l'étude d'un nouvel acces aux amines primaires sous leurs formes protégées par un groupe phtalimide par voie radicalaire. Une voie a été mise au point pour la synthèse du xanthate via une étape de bromation radicalaire au NBS.



La deuxième partie concerne l'étude d'un nouvel accès aux diamines sous leurs formes protégées par additions radicalairs.



De plus, M. Songzhe Han a rapporté un nouvel accès aux *N*-Boc 4-aminométhyl-pyrroles via une addition radicalaire de divers xanthates sur l'*N* –Boc azétine Boc suivie d'une aminolyse des adduits radicalairs obtenus.



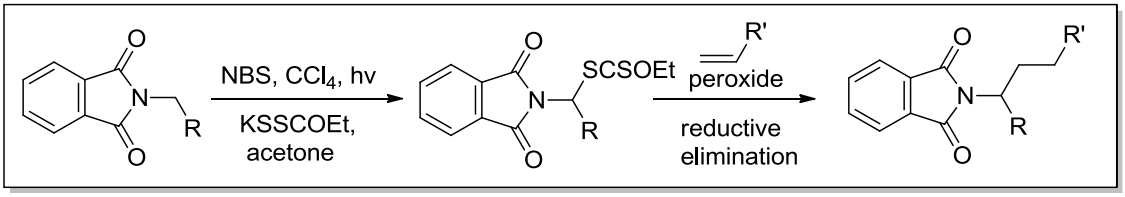
General Introduction

General Introduction

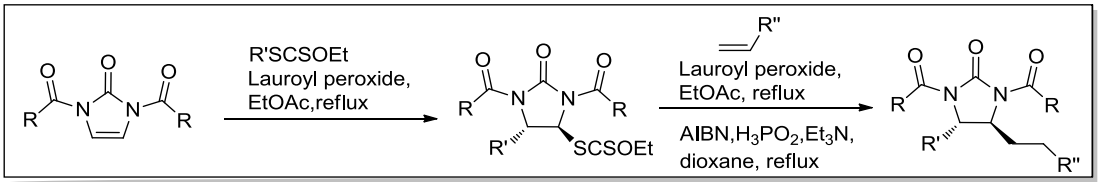
In chapter 1, general aspects of radical chemistry are briefly introduced. Improvements and applications of the Barton radical decarboxylation, the Barton-McCombie radical deoxygenation and the radical chemistry of xanthates are also described in this chapter.

In chapter 2, various methods for the construction of amines and especially radical hydroaminomethylation reaction developed in our group are described.

In chapter 3, based on our previous experiences of radical hydroaminomethylation reactions, the synthesis of protected amines, 1,3-diamines, β-aminoacids involving in another radical process, the Wohl-Ziegler reaction, will be described.

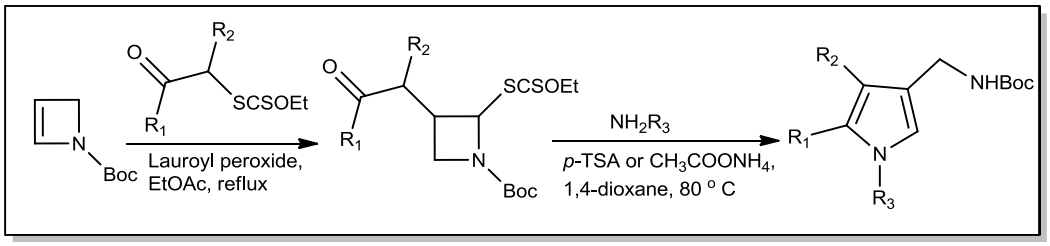


In chapter 4, a modular approach to access highly complex protected 1,2-diamines via the degenerative transfer of xanthates to protected 1,2-diamino alkenes will be described. Several extensions to prepare mono-protected diamines or indoline bearing diamino-unit will also be mentioned.



In chapter 5, we will describe a newly developed modular approach to access highly

substituted Boc-protected 4-aminomethyl-pyrroles via a radical addition of various *α*-xanthyl ketones to Boc-protected azetine following by the aminolysis of adducts. Therefore, plentiful functionalities can be incorporated into the final pyrrole products either through a xanthate partner or through ammonia or a primary amine.



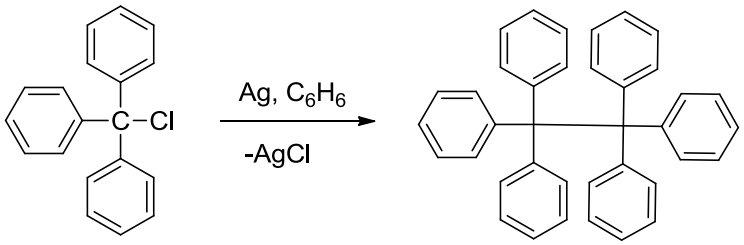
Chapter 1

Introduction of Radical Chemistry Associated with Thiocarbonyl Groups

Introduction

Generally, a free radical is an atom, molecule, or ion that bears an unpaired electron. Compared with a bonding or non-bonding electron pair possessing two electrons with opposite spins, +1/2 and -1/2, in one orbital according to Pauli's exclusion principle, a free radical has a single electron, which is alone in one orbital.

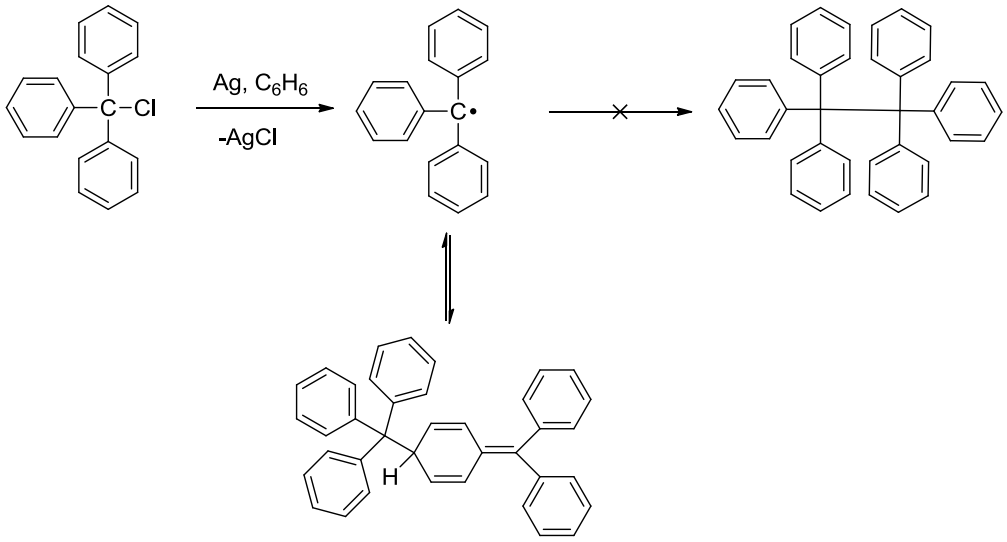
Historically, the first organic free radical triphenylmethyl was found and studied by Gomberg in 1900 at the University of Michigan when he attempted the synthesis of hexaphenylethane.[1] The triphenylmethyl radical is a persistent radical, which could be prepared by homolysis of triphenylmethyl chloride (Scheme 1.1) by silver metal in benzene as the solvent.



Scheme 1.1 Radical reaction of triphenylmethyl chloride

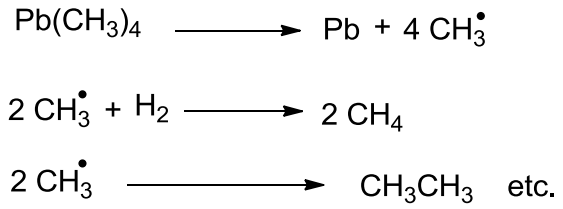
However, hexaphenylethane was in fact never prepared and the correct structure for the dimer was not fully determined until researchers at the Vrije Universiteit Amsterdam published their proton NMR data. Because of steric hindrance the triphenylmethyl radical does not dimerize in the expected manner (Scheme 1.2).[2]

[1] Gomberg. M. *J. Am. Chem. Soc.* **1900**, *22*, 757.
[2] Lankamp, H.; Nauta, W. Th.; MacLean, C. *Tetrahedron. Lett.* **1968**, *9*, 249.



Scheme 1.2

In 1929, the existence of the methyl radical was first demonstrated by Paneth and Hofeditz by thermal decomposition of tetramethyl lead (Scheme 1.3).[3] When the vapours of tetramethyllead mixed with gaseous hydrogen were passed through a hot silica tube at low pressure, the tetramethyl lead was decomposed and a mirror of metallic lead deposited on the internal surface of the tube.



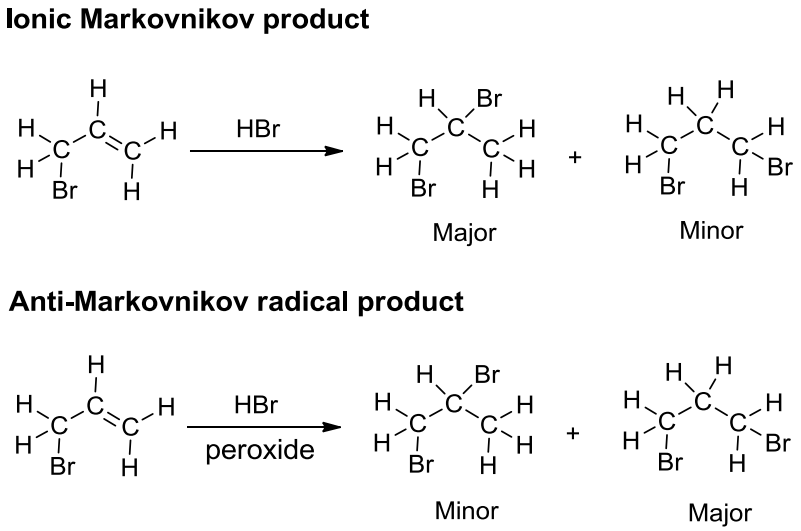
Scheme 1.3 Decomposition of tetramethyl lead

In 1933, a paper entitled "The addition of hydrogen bromide to allyl bromide" was published by Kharasch who for the first time proposed that the anti-Markovnikov addition of HBr to allyl bromide to yield 1,3-dibromopropane was due to the presence of peroxides and proceeded by a radical chain process. This was termed the "peroxide effect".[4] In order to find the direct evidence to support this idea, Kharasch performed

[3] Paneth, F.; Hofeditz, F. *Ber*. **1929**, *62*, 1335.

[4] Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc.* **1933**, *55*, 2468.

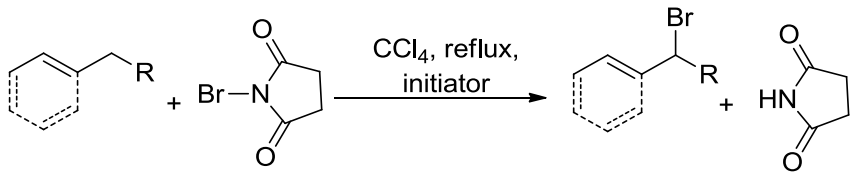
an adapted version of the thiocyanate test, an analytical test that is often employed to check shelf-stored reagents for their peroxide content. Moreover, by adding the antioxidants to reduce the radicals in the reaction mixture which caused the slow formation of 1,2-dibromopropane, this idea was further supported. Therefore, comparing with ionic Markovnikov process the large bromine atom was more probable to react with the least substituted carbon to produce a stable secondary radical instead of a primary radical, which resulted in the formation of anti Markovnikov product as the major product (Scheme 1.4).



Scheme 1.4 Markovnikov and Anti-Markovnikov reactions

The direct introduction of a halogen atom (bromine) in the allylic position of an olefin was first reported by Wohl; however, his papers did not attract much attention. Two decades later, Ziegler extensively studied the allylic bromination of olefins which involved the use of *N*-bromosuccinimide as a more convenient brominating agent (Scheme 1.5).[5] Normally, the best yields were obtained when the reaction was carried out in carbon tetrachloride with *N*-bromosuccinimide.

[5] (a) Wohl, A. *Ber*. **1919**, *52*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber.* **1921**, *54*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Ann*. **1942**, *551*, 80. (d) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573.



Scheme 1.5 Wohl-Ziegler reaction

Since the Electron paramagnetic resonance effect was first observed in Kazan State University by Soviet physicist Yevgeny Zavoisky in 1944, scientists could detect radicals directly by this technique which further promoted the development of radical chemistry.[6]

In 1975, the Barton-McComie deoxygenation of alcohols,[7] followed later by the Barton decarboxylation of carboxylic acids[8] and other powerful reactions involving a radical chain process were reported, which opened up numerous possibilities for the application of radical chemistry in organic synthesis. In this chapter, several general concepts of radical chemistry will be mentioned. The Barton radical decarboxylation and the Barton-McCombie radical deoxygenation as two of the most important radical reactions will be briefly introduced. Finally, we will go through other thiocarbonyl related radical reactions and the xanthate chemistry developed in our group.

[6] Schweiger, A.; Jeschke, G. *Principles of Pulse Electron Paramagnetic Resonance;* **2001**. Oxford University Press.
[7] Barton, D. H. R.; Mcombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
[8] Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939.

I. General aspects of free radicals

1. Radical types

Generally, organic free radicals are quite reactive and unstable species and can be divided into two kinds, neutral radicals and charged radicals (neutral radical, radical cation and radical anion) (Figure 1.1).

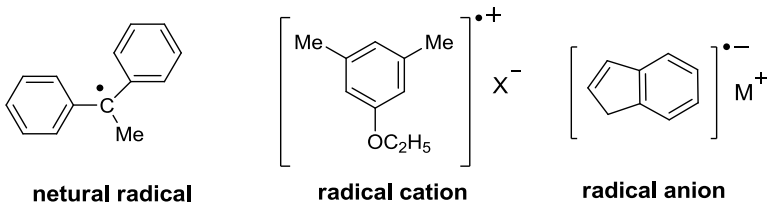


Figure 1.1 Neutral radicals and charged radicals

Moreover, depending to whether the unpaired electron is in sp^x (x=1, 2, 3) σ or in p orbital, two different types of radicals, σ radical and π radical, can be defined. A phenyl radical is a typical σ radical and a *tert*-butyl radical is a typical π radical (Figure 1.2).

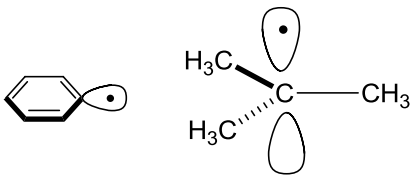
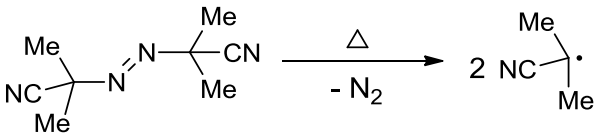


Figure 1.2 σ And π radicals

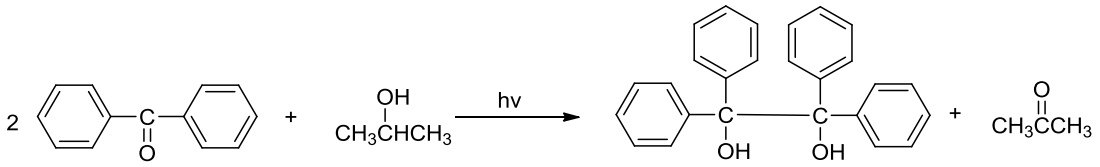
2. Generation of radicals

The radical can be generated by heating, by irradiation or by single electron transfer. As shown in Scheme 1.6, azobisisobutyronitrile, one of the most common radical initiators, generates a molecule of nitrogen gas and two 2-cyanoprop-2-yl radicals upon moderate heating (half-life = 1h at 85 ℃).



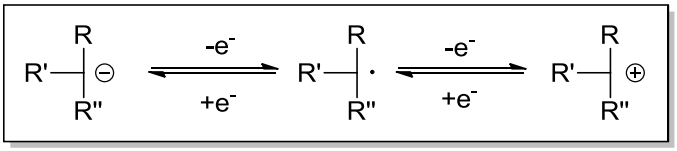
Scheme 1.6. Thermolysis of azobisisobutyronitrile (AIBN)

In the case of the photoinduced radical reaction shown in Scheme 1.7, irradiation causes the homolysis of the carbon-oxygen π-bond and leads to the formation of biradical intermediate which readily abstracts hydrogen from isopropanol to form the corresponding diol product.



Scheme 1.7 Photoinduced radical reaction

As shown in Scheme 1.8, single electron transfer from an electron-rich species (anion) or one electron addition to electron deficient species (cation) is a quite efficient approach to generate radicals (redox processes). [9]

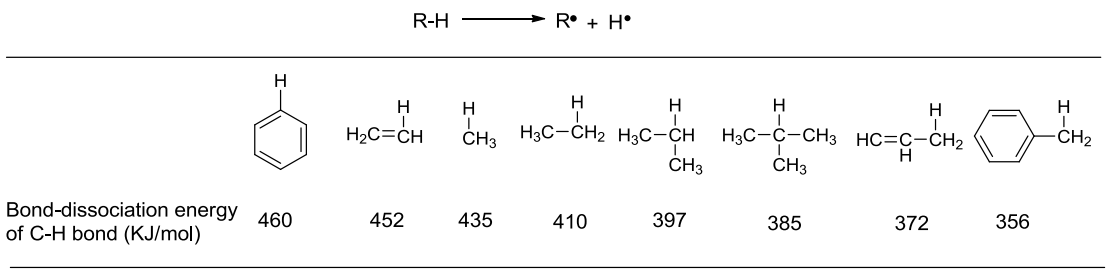


Scheme 1.8 Single electron transfer

3. Radical stability

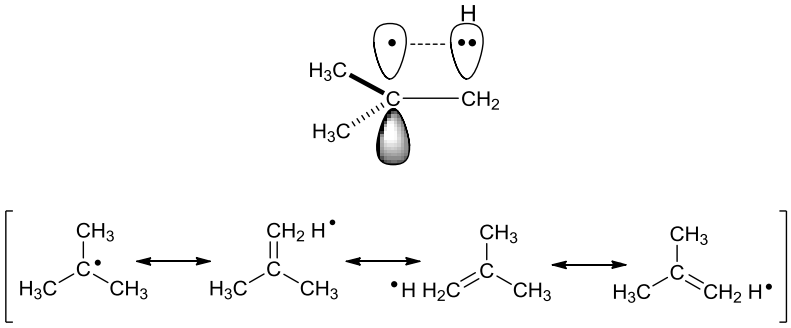
The considerable difference in bond dissociation energies between the starting materials and the products is the main driving force leading to the formation and ratio of products. Therefore, the bond dissociation energy can reflect the different stabilities of radicals. As shown in Scheme 1.9, a lower bond dissociation energy of a carbon-hydrogen bond generally corresponds a more stable carbon radical.

[9] Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579.



Scheme 1.9 Bond dissociation energies

As illustrated in Scheme 10, the resonance structures of *tert*-butyl radical illustrates how hyperconjugation effect stabilizes the *tert*-butyl radical. The overlap between the σ orbital of an adjacent C-H bond with the *p*-orbital holding the single electron results in a stablising 3-electron interaction.



Scheme 1.10 Hyperconjugation effect

Comparing the stability of most common carbon radicals in Figure 1.3, the hyperconjugation effect well explains the reason why higher substituted π-radicals are, in general, more stable than low substituted ones. However, no such stabilizing effect exists for phenyl or vinyl radicals, which leads to their higher bond dissociation energies as shown in Scheme 1.9.

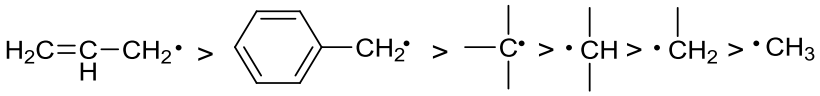
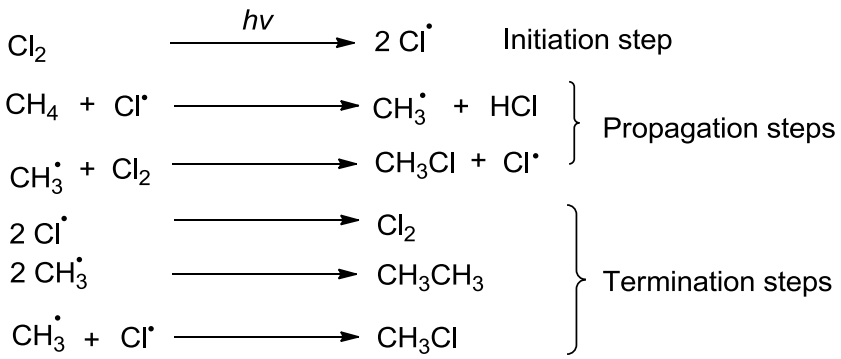


Figure 1.3 Allylic, benzylic > tertiary > secondary > primary > methyl radicals

4. Free radical chain processes

A free radical chain process can be divided into three types: initiation, propagation and termination. The halogenation of methane is one typical example shown in Scheme 1.11 that explains how radicals act in each step.[10] In the initiation step, the homolysis by irradiation of the chlorine-chlorine bond gives two chlorine atoms. In the following propagation step, the chlorine radical abstracts hydrogen from methane to form a methyl radical and this methyl radical readily attacks chlorine to form a new chlorine atom to sustain this radical chain process. Finally, the combinations between different radicals result in the termination of this chain process. This whole process is defined as a free radical chain process.



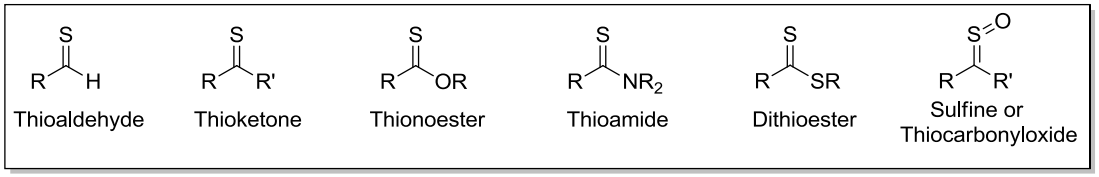
Scheme 1.11 Halogenation of methane

[10] Rossberg, M. et al. *Chlorinated Hydrocarbons in Ullmann's Encyclopedia of Industrial Chemistry*, **2006**, Wiley-VCH, Weinheim.

Π. The Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

1. Thiocarbonyl compounds and their structural properties

The structures and nomenclature of various thiocarbonyl compounds are displayed in Scheme 1.12. Compared with their carbonyl (oxygen) analogs, the larger covalent radius of sulfur vs oxygen (104.9 nm vs 70.2 nm), higher polarizability of sulfur relative to oxygen, less efficient overlap and lower coefficient of S_{3p}-C_{2p} π-bond together lead to the lower dissociation energy of the C=S bond (115 kcal/mol) than the C=O bond (162 kcal/mol). Therefore, thiocarbonyl compounds typically display greater reactivity in either ionic or radical reactions.



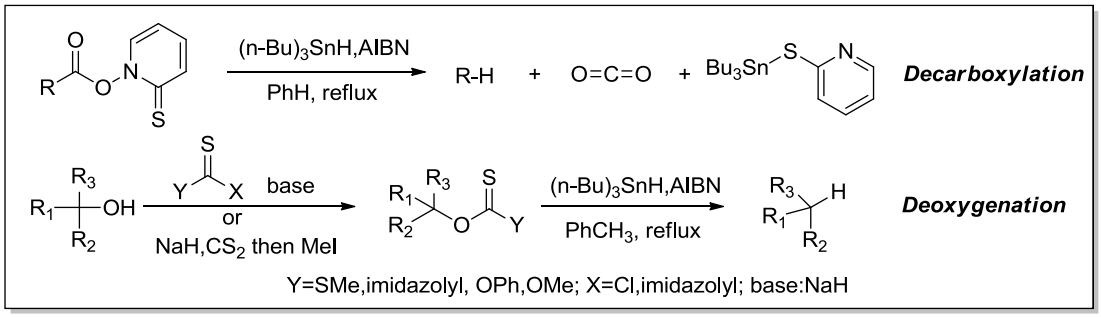
Scheme 1.12 Thiocarbonyl compounds

In radical reactions, thiocarbonyl compounds are generally radicophilic species that efficiently scavenge radical intermediates. This unique structure feature of thiocarbonyl group leads to a rich and varied radical chemistry. Besides the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation, other thiocarbonyl compounds related radical reactions are being studied. In particular, the exchange of xanthates and related dithiocarbonyl derivatives, which will be discussed later, has proved to be especially useful in the context of the general effort to design tin-free processes.

2. Reaction pathway of the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

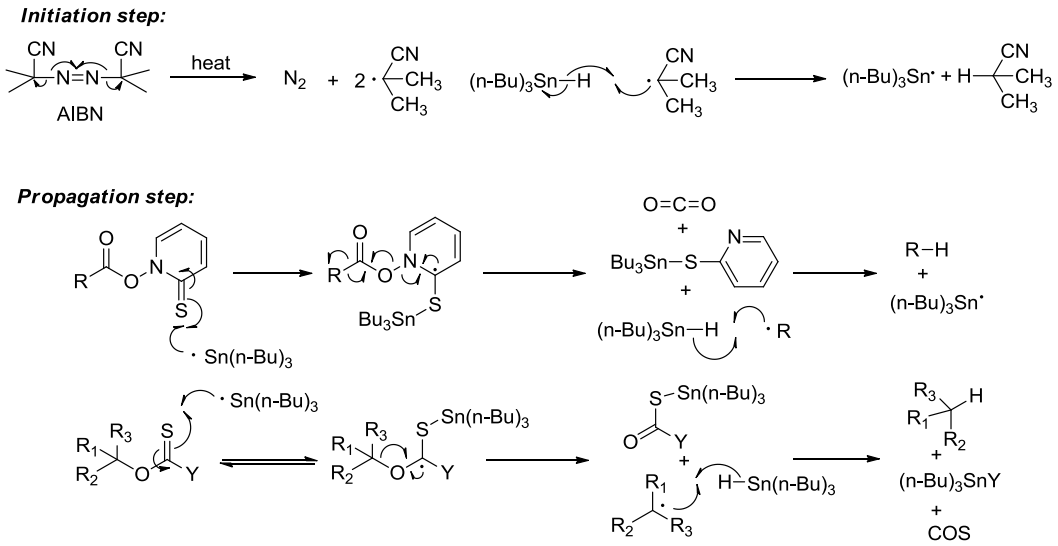
The Barton radical decarboxylation[8] and the Barton-McCombie radical

deoxygenation[7] reactions as two of the most powerful radical reactions, reported by Barton and his co-workers in 1983 and since 1975 respectively. To better understand the similarities and differences of the two reactions, their general equations are pictured in Scheme 1.13. In the Barton decarboxylation, by using tri-*n*-butyltin hydride as the hydrogen atom donor, the reductive decarboxylation product is formed through the thiohydroxamate ester intermediate known as Barton ester. Tri-*n*-butyltin hydride as the hydrogen donor is also used in the Barton-McCombie deoxygenation process which involves reaction with thionoester derivatives of the alcohol.



Scheme 1.13 Barton decarboxylation and Barton-McCombie deoxygenation

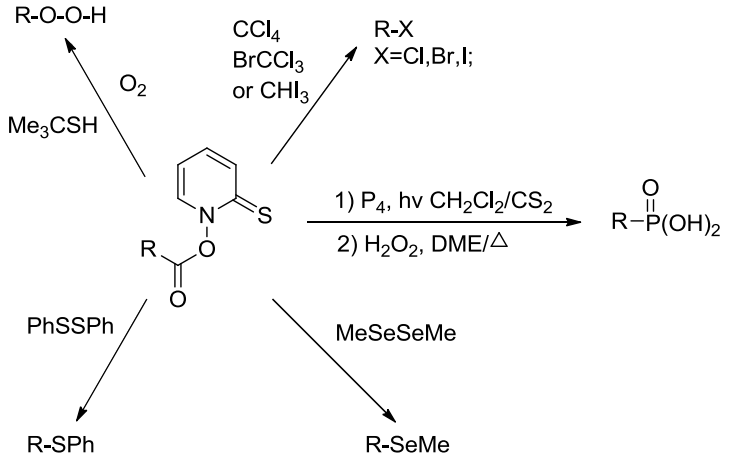
The mechanisms proposed for these transformations are displayed in Scheme 1.14. Both may involve the use of AIBN as the initiator allowing the generation of the starting tri-*n*-butyltin radicals. In their propagation steps, the radicophilicity of the thiono group encourages rapid attack by tri-*n*-butyltin radical to form a strong Sn-S bond. Finally, carbon dioxide is lost in the Barton decarboxylation process to afford the reduced product by abstraction of a hydrogen atom from tri-*n*-butyltin hydride; in the case of the Barton-McCombie deoxygenation, the fragmentation of the intermediate and hydrogen atom abstraction gives the deoxygenated product. .



Scheme 1.14 Mechanism of the Barton decarboxylation and deoxygenation

3. Applications of the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction in organic synthesis

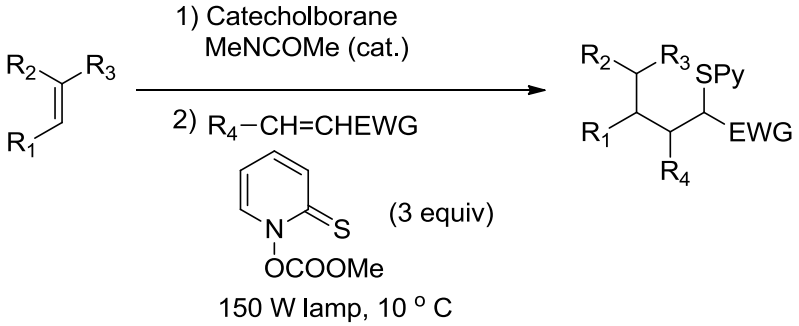
A carboxylic acid group can be converted into various other functional groups via its thiohydroxamate ester intermediate based on the Barton radical decarboxylation reaction. As illustrated in Scheme 1.15, the formation of a carbon-oxygen bond, a carbon-halogen bond, a carbon-sulfur bond, carbon-selenium bond or a carbon-phosphorus can be readily accomplished.[11]



Scheme 1.15 Synthetic variations of the Barton radical decarboxylation

[11] Chimiak, A.; Przychodzen, W.; Rachon, J. *Heteroat. Chem.* **2002**, *13*, 169.

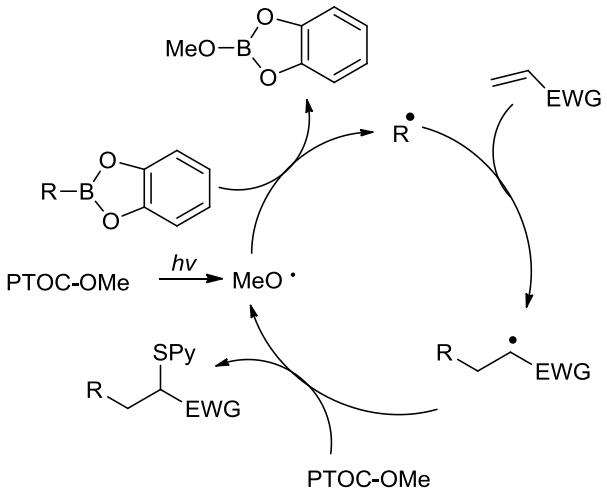
In 2000, a radical conjugate addition process was reported by Renaud and co-workers.[12] As illustrated in Scheme 1.16, the radical addition of an alkylborane to an alkene bearing an electron withdrawing group to furnish the corresponding adduct bearing an *S*-pyridyl group was accomplished through the irradiation of the Barton carbonate PTOC-OMe (PTOC = pyridine-2-thione-*N*-oxycarbonyl) with a 150 W tungsten lamp.



Scheme 1.16 Radical conjugate addition

The reaction pathway is described in Scheme 1.17. The hydroboration of the alkene substrate gives the corresponding alkylborane. In the second step, a methoxyl radical is generated upon photolysis of the Barton carbonate PTOC-OMe with a 150 W tungsten lamp. The methoxyl radical readily reacts with the alkylborane to form an alky radical. As a nucleophilic radical, the alky radical undergoes the radical addition with alkene bearing electron withdrawing group to generate an electrophilic radical. This electrophilic radical intermediate then reacts with another molecule PTOC-OMe to form the desired product bearing an *S*-pyridyl group and another methoxyl radical to sustain this radical chain process. Since the product bearing an *S*-pyridyl group, it can be removed or converted into other functional groups using the rich chemistry of sulfides.

[12] Ollivier, C.; Renaud, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 925.



Scheme 1.17 Mechanism of radical conjugate addition

4. Improvements in the Barton radical decarboxylation and the Barton-McCombie radical deoxygenation reaction

Although the Barton decarboxylation and the Barton-McCombie deoxygenation are widely applied in organic synthesis, the drawbacks still remain in both of the two reactions. For instance, the difficulty in removing the organotin residues from the end products makes the techniques using tin inappropriate for the syntheses of drugs, medicines, and other formulations intended for human consumption.

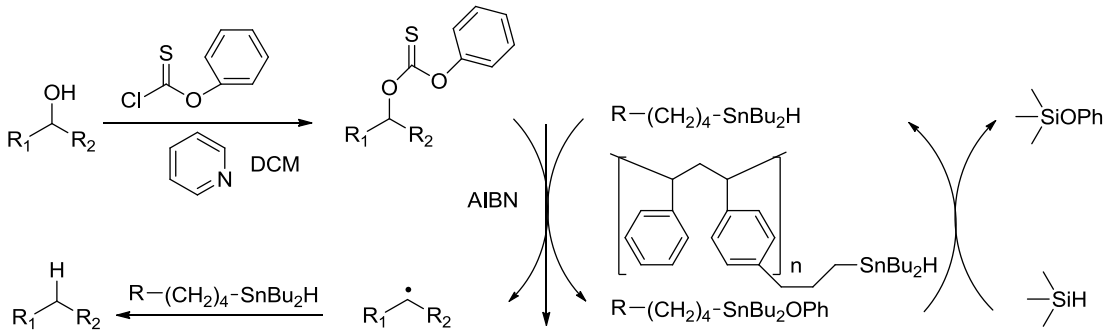
4.1. Modification of organotins and their applications in radical reactions

The tedious purification of reaction mixtures involving stoichiometric tin hydride is a major drawback. In order to easily remove organotin from the desired products, various workup procedures or modification of the structure of the tin hydride have been developed.

For instance, in 2000, Dumartin and co-workers reported a Barton-McCombie process employing a catalytic amount of supported tin hydride in the presence of trimethoxysilane (Scheme 1.18).[13] Since silane rapidly reacts with Sn-OR bonds to give new tin hydride bonds, the regeneration of tin hydride is accomplished via this

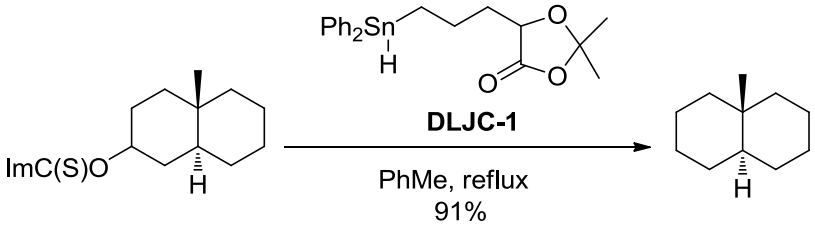
[13] Boussaguet, P.; Delmond, B.; Dumartin, G.; Pereyre, M. *Tetrahedron. Lett.* **2000**, *41*, 3377.

method.



Scheme 1.18 Regeneration of tin hydride

In 2002, the stannane **DLJC-1** was designed as a replacement of tri-*n*-butyltin hydride by Clive and co-workers (Scheme 1.19).[14] The stannane **DLJC-1** can be hydrolyzed by LiOH-water-THF or TsOH-water-THF to form the base-soluble materials which apparently simplifies the separation of desired products from the tin-containing byproducts.



Scheme 1.19 Stannane **DLJC-1** in Barton-McCombie radical deoxygenation reaction

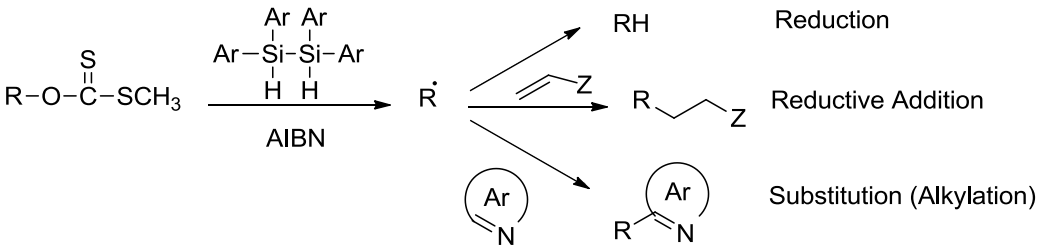
4.2. Tin-free Barton decarboxylations and Barton-McCombie deoxygenation radical reactions

The high toxicity of organotin compounds demands chemists to reduce or even avoid the usage of organotin reagents. In some cases, catalytic amounts of tin hydride are required, so stoichiometric amounts of another reducing agents such as poly(methylhydrosiloxane), sodium borohydride, and cyanoborohydride are employed

[14] Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1192.

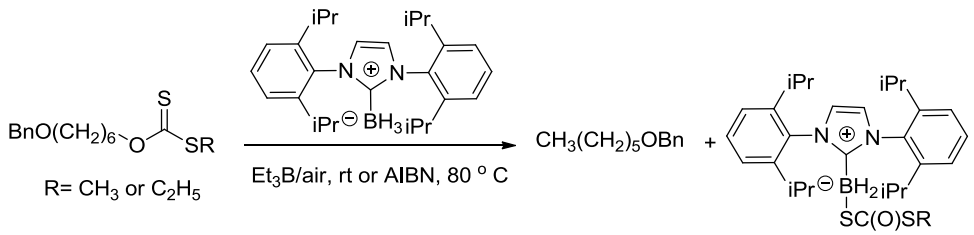
to accomplish this process. However, it is more interesting to avoid the organotin derivatives altogether by devising more acceptable replacements such silanes, dialkyl phosphinates and hypophosporous acid and its salts.

Barton-McCombie deoxygenations involving the utilization of tetraphenyl--disilane instead of organotin were reported by Togo and co-workers in 2000.[15] As shown in Scheme 1.20, the reductive removal of the xanthate group and related reductive additions or alkylations could be accomplished using tetraphenyldisilane as the hydrogen atom donor.



Scheme 1.20 Reductive elimination of xanthate group by using tetraphenyldisilane

Recently, the reduction of xanthate by *N*-heterocyclic carbene boranes (NHC-boranes) hitherto unknown NHC-boryl radicals was reported by Curran and co-workers (Scheme 1.21).[16] Furthermore, they estimated the reaction rate of the reduction step involving NHC-borane to be 2 orders of magnitude slower than with Bu_3SnH and 1 order of magnitude slower than $(TMS)_3SiH$.



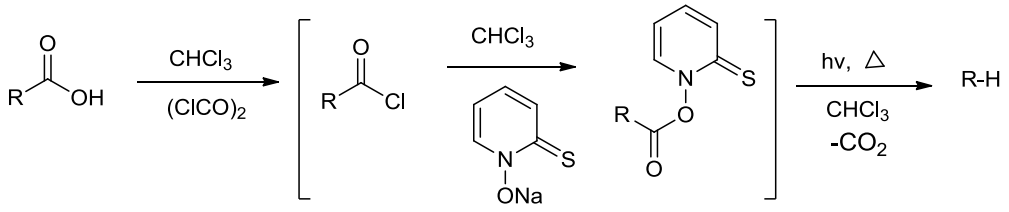
Scheme 1.21 Reductive elimination of xanthate group by using NHC-boranes

Besides tetraphenyldisilane, NHC-borane and their related derivatives,

[15] Togo, H.; Matsubayashi, S.; Yamazaki, O.; Yokoyama, M. *J. Org. Chem.* **2000**, *65*, 2816.

[16] Ueng, S. H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256.

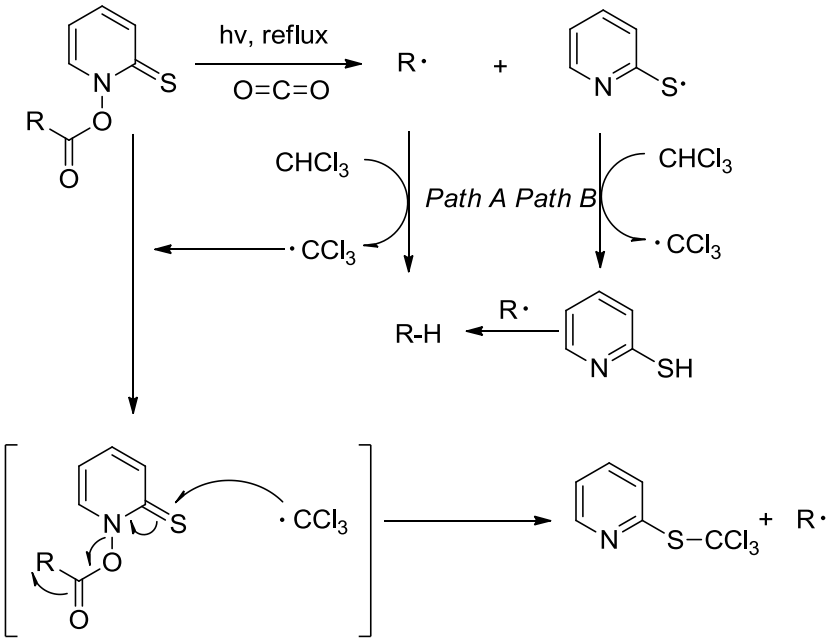
chloroform as solvent can also act as a hydrogen atom donor in the Barton decarboxylation process, as was discovered by Tsanaktsidis and co-workers in 2011.[17] As shown in Scheme 1.22, the irradiation of thiohydroxamate ester in chloroform gave the corresponding reduced product.



Scheme 1.22 Chloroform as a hydrogen atom donor in the Barton decarboxylation

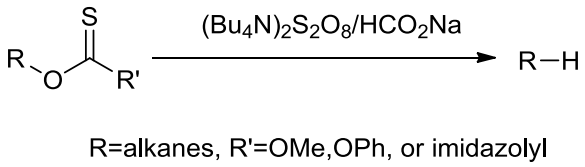
Accordingly, two plausible mechanism pathways A and B were proposed as displayed in Scheme 1.23. The thiohydroxamate ester loses carbon dioxide to generate the alkyl radical. Then, in path A, the alkyl radical abstracts a hydrogen atom from chloroform to form the reduction product. In path B, 2-pyridylthiyl radical as an electrophilic radical prefers to abstract a hydrogen atom from chloroform to form a nucleophilic radical. The hydrogen transfer between 2-pyridylthiyl radical and chloroform in path B is consistent with the concept of polarity reversal catalysis.[18] Both of the reductive reactions in path A or B would result in the formation of a trichloromethyl radical to sustain this radical process.

[17] Ko, J. E.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. *Org. Lett.* **2011**, *13*, 1944.
[18] Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.



Scheme 1.23 Plausible mechanism

Although the replacements of organotin hydrides by other hydrogen atom donors can improve the applications of related radical reactions, limitations like cost, availability, and toxicity still remain in the above replacements. In 2005, an efficient tin-free Barton-McCombie radical deoxygenation involving a redox process was accomplished by Kim and co-workers.[19] As illustrated in Scheme 1.24, readily available sodium formate and tetrabutylammonium peroxydisulfate were used as the reducing combination.

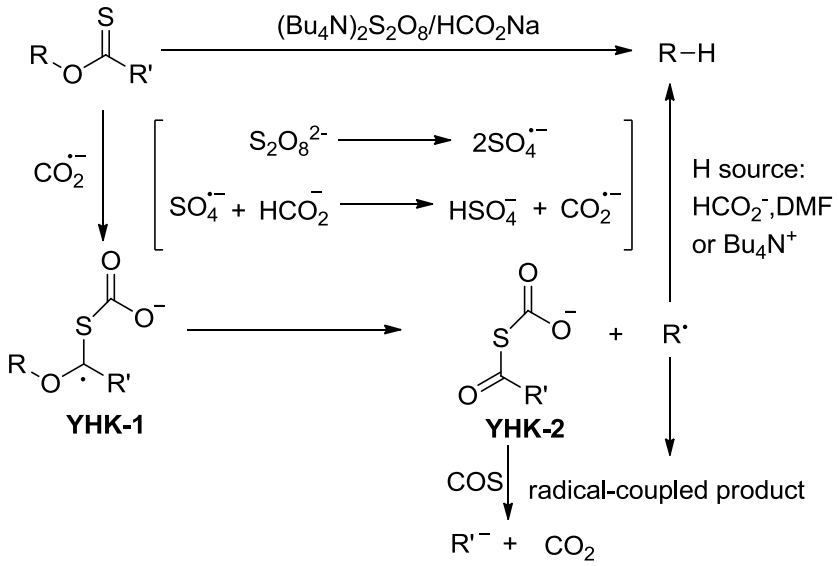


Scheme 1.24 Barton-McCombie radical deoxygenation via a redox process

A plausible mechanism is shown in Scheme 1.25. It assumes that the transfer of a single electron to thiocarbonyl derivatives takes place from carbon dioxide radical anion rather than $SO_4^{\bullet-}$. The radical addition of carbon dioxide radical anion to the thiocarbonyl substrate gives the radical intermediate **YHK-1**. The formation of anion

[19] Park, H. S.; Lee, Y. H.; Kim, Y. H. *Org. Lett.* **2005**, *7*, 3187.

YHK-2 and R radical occur with the loss of COS from **YHK-1**. Finally, the R radical abstracts a hydrogen atom from a hydrogen source to furnish the corresponding deoxygenated product.



Scheme 1.25 Plausible mechanism

III. Degenerative transfer of xanthates

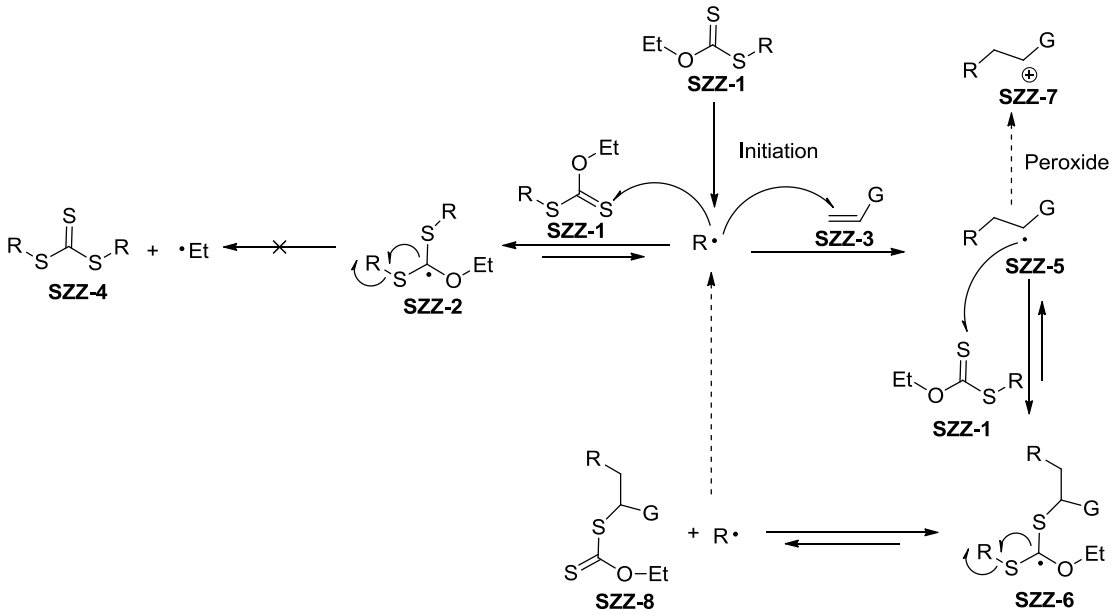
Since the cleavage of carbon-sulfur bond taking place under metal free conditions was found by Zard, the degenerative radical addition transfer of xanthates onto alkenes was systematically investigated by Zard and co-workers during the past decades. This process allows numerous hitherto difficult inter- or intramolecular addition of xanthates to olefins and represents a highly efficient approach to numerous functionalized structures.[20]

1. Mechanism

The mechanistic pathway of the degenerative transfer of xanthates onto alkenes is outlined in Scheme 1.26. In the initiation step, the cleavage of C-S bond of xanthate **SZZ-1** gives an R radical which may either reversibly add to the sulfur atom of another xanthate or add to the alkene. There are two possible pathways in the following steps: either the adduct **SZZ-2** gives **SZZ-4** by generating a high energy ethyl radical or adduct **SZZ-5** attacks the sulfur atom to form another adduct **SZZ-6** in a reversible manner. By contrast, due to the high energy of ethyl radical the former pathway is unlikely. Therefore, radical intermediate **SZZ-6** is formed and then its collapse leads to the formation of corresponding product **SZZ-8** and another R radical to sustain this radical chain process. It is worthwhile to note that the formation of **SZZ-2**, **SZZ-6** or **SZZ-8** is a reversible process. Therefore, even under high concentration of xanthate, the newly formed R radicals could be converted to **SZZ-2** or **SZZ-6** which act as reservoirs for active radicals and lower their concentration in the medium, thus limiting radical-radical interaction. However, we should also notice that excess amounts of peroxide may oxidize the radical intermediate **SZZ-5** to form a cation **SZZ-7** which may be exploited in certain transformations. Finally, a higher

[20] For reviews on the xanthate radical addition-transfer process, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (f) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

stability of the R radical as compared with the adduct radical **SZZ-5** is an essential to keep the chain process efficient. Otherwise, if the stability of the R radical is lower than that adduct radical **SZZ-5** then oligomers tend to form and process remains difficult to control.

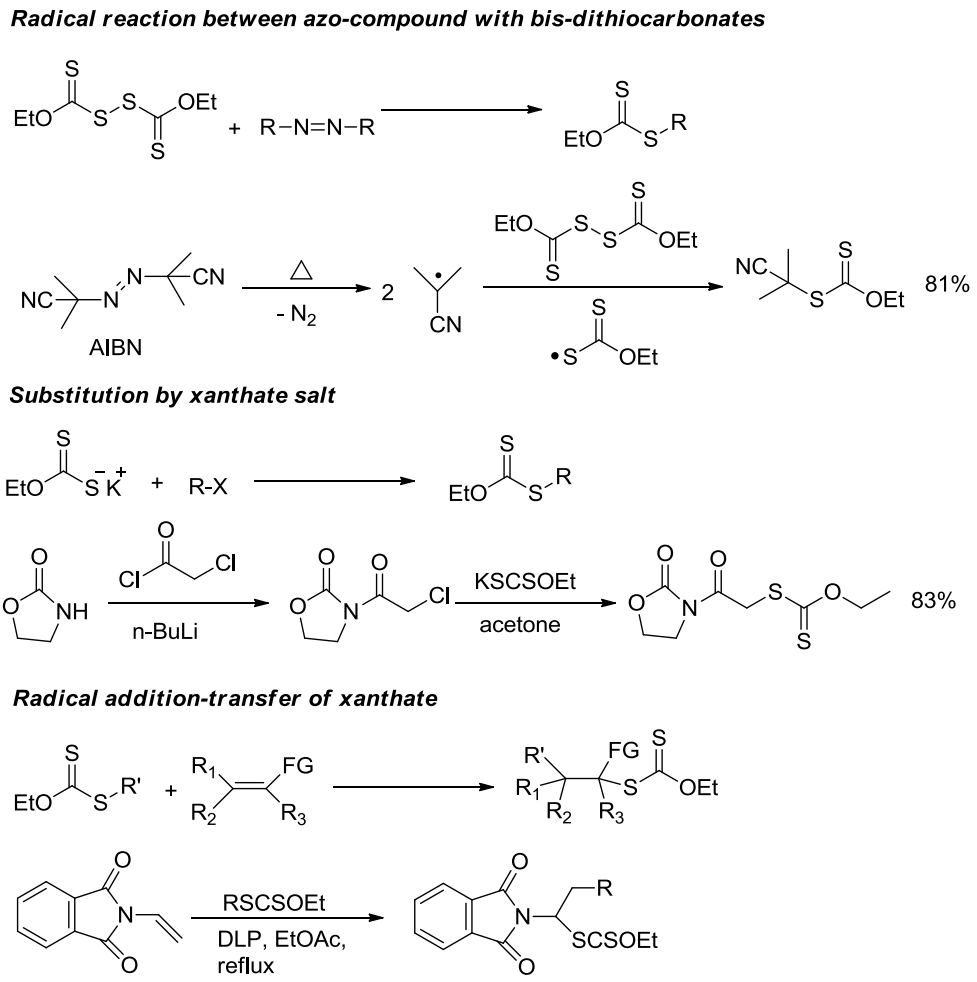


Scheme 1.26 Mechanisms of the degenerative addition transfer of xanthates onto alkenes

2. Preparation

There have been several methods to prepare various types of xanthates, three of them with corresponding examples are presented in Scheme 1.27.[21] Xanthates can be readily obtained by the reaction of a xanthate salt with an alkylating agent, or the reaction of an azo-compound with bis-dithiocarbonates, or by radical addition-transfer of a xanthate onto an alkene.

[21] (a) Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **1999**, *40*, 277. (b) Thang, S.; Chong, Y.; Mayadunne, R.; Moad, G.; Rizzardo, E. *Tetrahedron Lett.* **1999**, *40*, 2435. (c) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435. (d) Tanaka, K.; Tamura, N.; Kaji, A. *Chem. Lett.* **1980**, 595.



Scheme 1.27 Preparation of xanthates

3. Applications of degenerative addition-transfer of xanthate

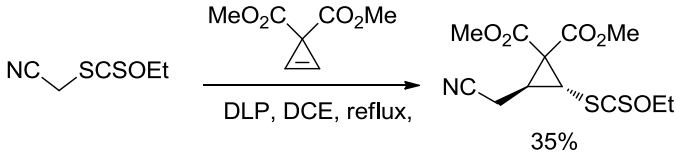
Since the discovery of this degenerative addition-transfer process, Zard and co-workers studied and explored the scope of this process extensively by applying this reaction to the preparation of diversely functionalized compounds. These applications demonstrate the advantages of the xanthate transfer reaction: 1. The xanthate starting material can be readily obtained from cheap potassium *O*-ethyl xanthate salt; 2. The xanthate transfer reaction is easily scaled up; 3. Normally, the reactions take place under mild, neutral reaction conditions and are initiated by the quite cheap dilauroyl peroxide in refluxing ethyl acetate; 4. The reactions are performed under metal-free conditions and are therefore ecologically acceptable

Generally, the degenerative addition-transfer of xanthates onto alkenes is used to bring together various functional groups or to construct complex ring systems via

radical cyclization reactions. These aspects will be described in the following reactions.

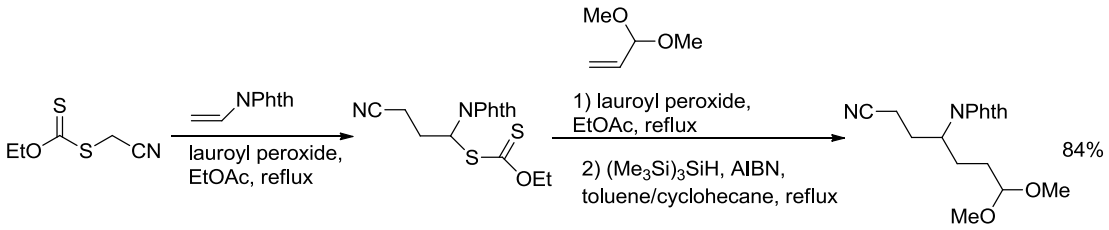
3.1. Radical additions

Radical addition of xanthate to unactivated olefins, inducing various strained olefins such as cyclopropenes, cyclobutenes, azetines and methylenecyclopropanes furnishes the corresponding adducts as shown by the example in Scheme 1.28.[22]



Scheme 1.28. Radical addition of a xanthate to a strained olefin

Another quite interesting application is the synthesis of protected primary amines via radical addition of a xanthate to *N*-vinylphthalimide to give an adduct which can undergo another radical addition to another olefin (Scheme 29).[23] Then the reductive removal of the xanthate group furnishes the corresponding protected primary amine, which can be considered as a radical hydroaminoalkylation process.[24]



Scheme 29. Radical addition of xanthate to *N*-vinylphthalimide

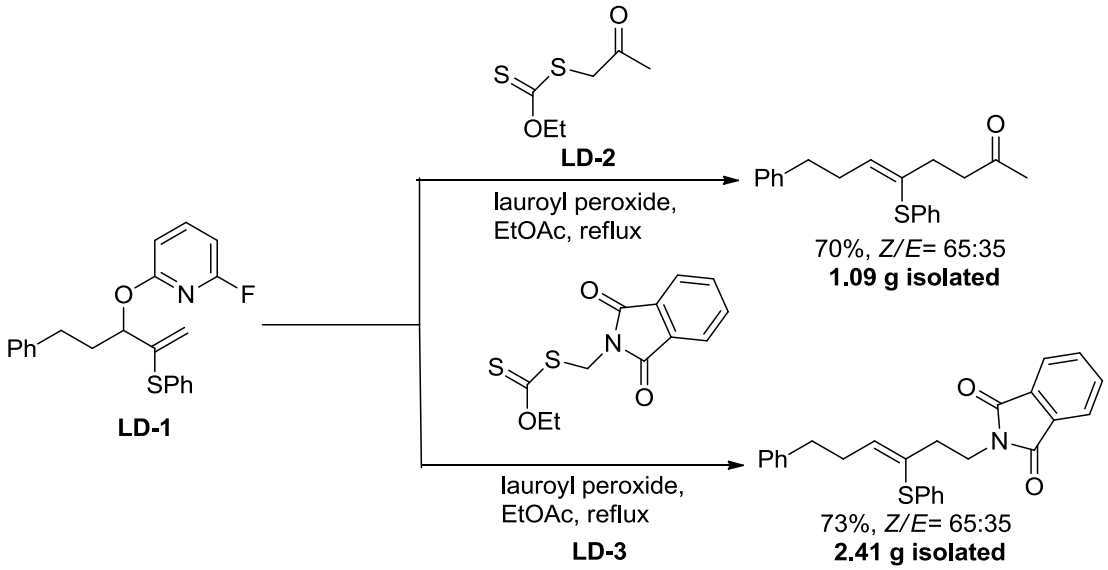
Recently, the group reported a mild and stereoselective synthesis of tri- and tetrasubstituted functionalized vinyl sulfides relying on the radical allylation of xanthates **LD-2** or **LD-3** with vinyl sulfide **LD-1** (Scheme 1.30), which undergoes a

[22] Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.

[23] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656.

[24] (a) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279. (b) Quiclet-Sire, B.; Revol G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 3554. (c) Quiclet-Sire, B.; Lebreux, F.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2844. (d) Quiclet-Sire, B.; Zard, S. Z. *Heterocycles* **2010**, *82*, 263.

radical addition elimination process.[25]



Scheme 1.30 Radical addition of xanthate to phenyl vinyl sulfones

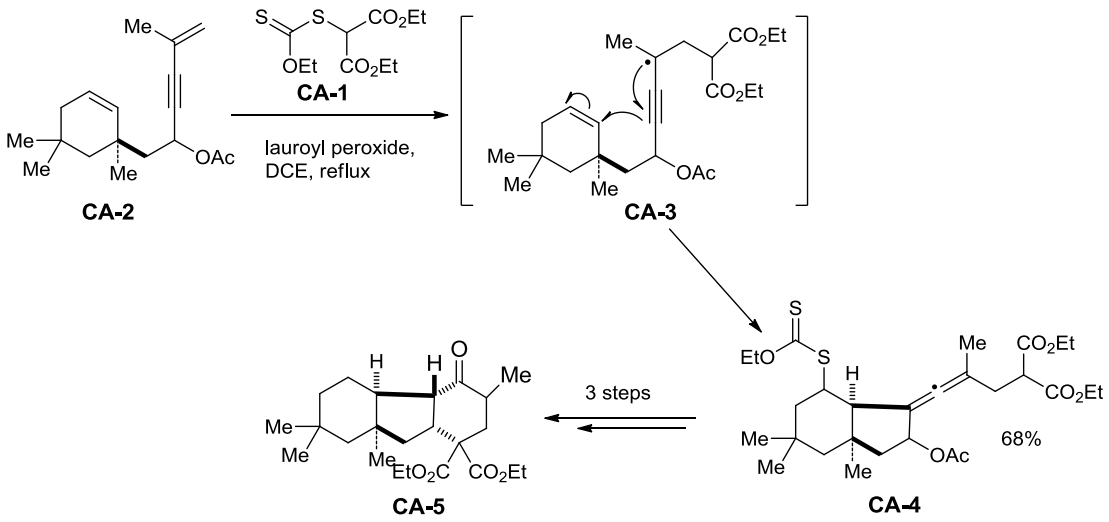
3.2. Radical cyclizations

Since heterocyclic compounds are ubiquitous and highly valuable in the pharmaceutical area and in material science it is more interesting to apply the xanthate technology for the construction of polycyclic structures.[26] As shown in Scheme 1.31, the addition of xanthate **CA-1** to enyne **CA-2** gives intermediate **CA-3** which undergoes cyclization to furnish a tetrasubstituted allene **CA-4** directly in high yield.[27] This allene can be further converted into a complex tricyclic compound bearing five chiral centers via three more steps.

[25] (a) Debien, L.; Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2013**, *15*, 6250. (b) Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

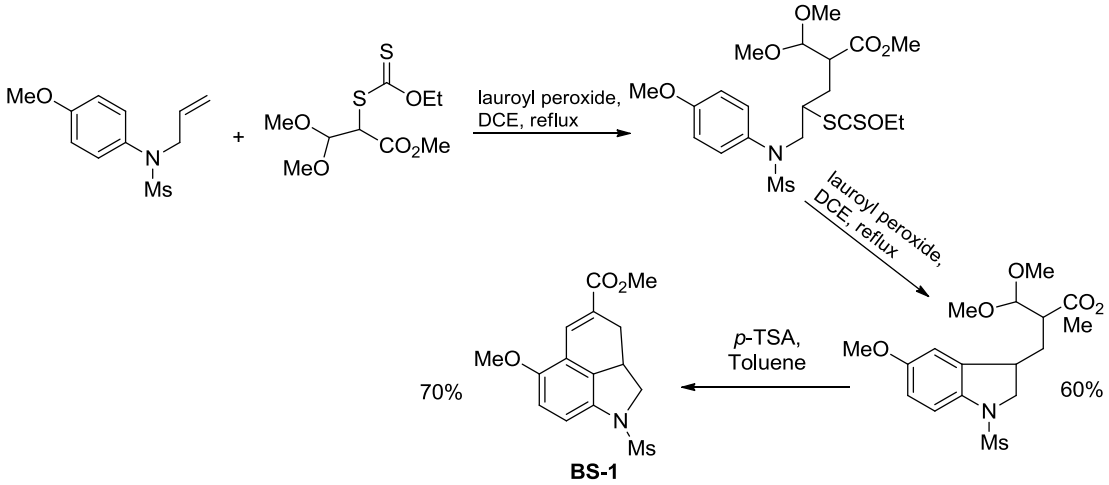
[26] Denieul, M.-P.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495.

[27] Alameda-Angulo, C.; Quiclet-Sire, B.; Zard. S. Z. *Tetrahedron Lett.* **2006**, *47*, 913.



Scheme 1.31 Synthesis of **CA-5**

The synthesis of tricyclic compound **BS-1** is described by Sortais.[28] It is outlined in Scheme 1.32 and consists in the combination of a radical addition and cyclization flowed by a second ionic ring-closure to finish tricyclic product **BS-1** in high yield.



Scheme 1.32 Synthesis of tricyclic compound **BS-1**

Some unusual heterocyclic compounds or even unknown classes of heterocycles can be prepared via the combination of radical reactions with ionic processes.[29] As shown in Scheme 1.33, the synthesis of both sulfone **PB-1**[30] and dihydrothiazines[31]

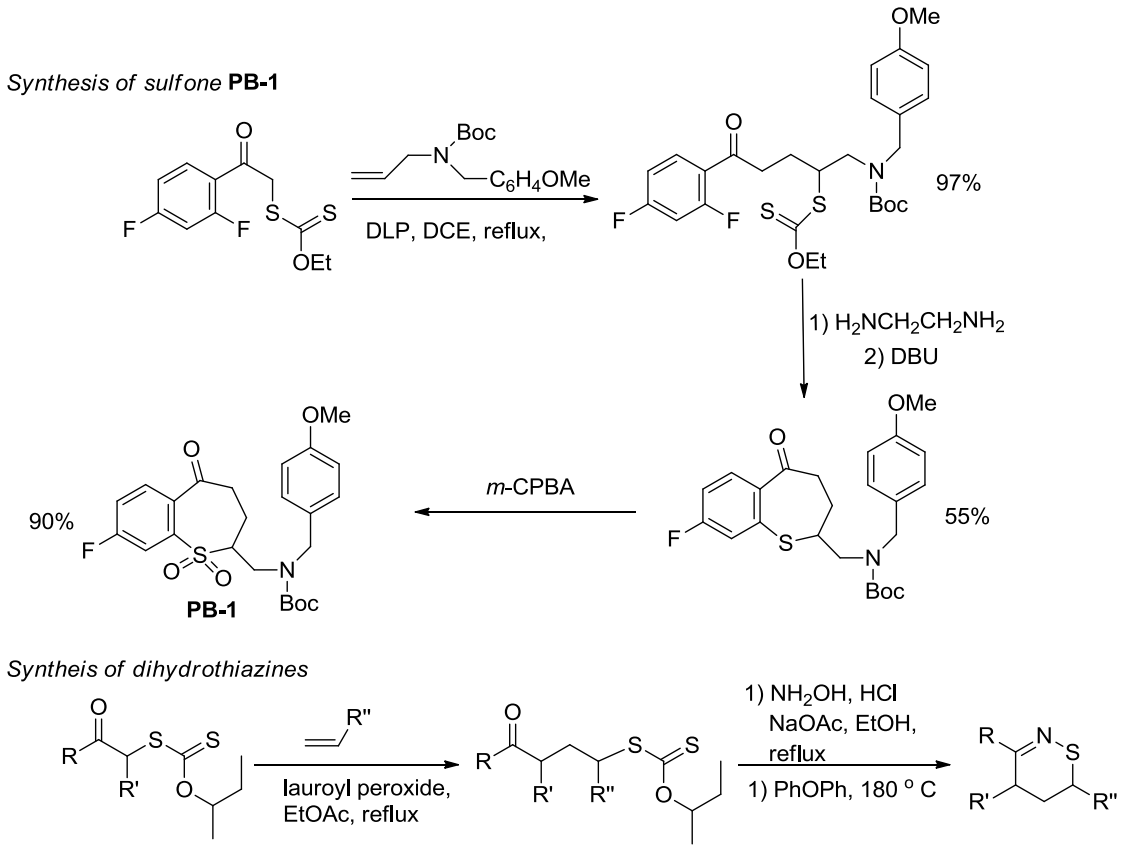
[28] Sortais. B.; Ph. D. Thesis, Ecole Polytechnique, Palaiseau, **2002**.

[29] For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

[30] Boutillier, P.; Quiclet-Sire, B.; Zafar, S. N.; Zard. S. Z. *Tetrahedron Asymmetry* **2010**, *21*, 1649.

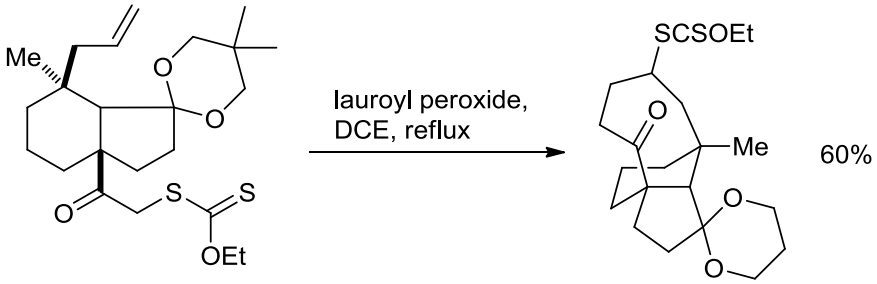
[31] Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2013**, *15*, 5886.

are accomplished via a radical addition- ionic cyclization process.



Scheme 1.33 Radical addition-ionic cyclization

Besides the preparation of different heterocyclic compounds, this technique was applied to a few total syntheses. As shown in Scheme 1.34, in an approach to the synthesis of the tricyclic skeleton of pleuromutilin, the intramolecular radical addition for the construction of an eight membered ring was accomplished in good yield.[32]



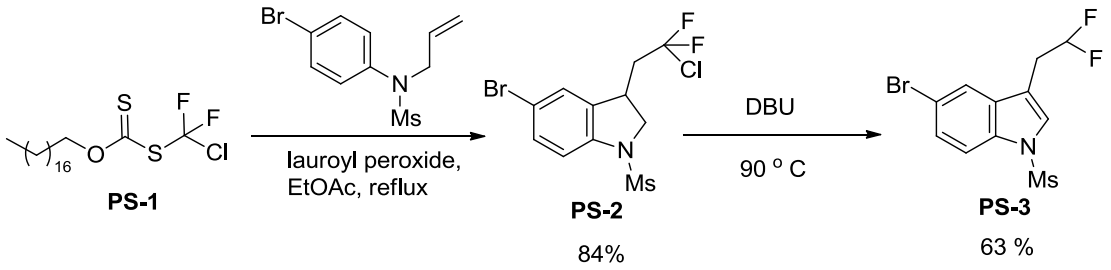
Scheme 1.34 Synthesis of tricyclic skeleton of pleuromutilin

[32] Kalai, C.; Tate, E.; Zard, S. Z. *Org. Lett.*, **2003**, *5*, 325.

3.3. Recent studies of degenerative addition-transfer

3.3.1. The synthesis of *gem*-difluoro compounds

There have been several applications of xanthates for the construction of organofluorine compounds.[33] Recently, Salomon reported the synthesis of *gem*-difluoroalkenes, -dienes and (2,2-difluoroethyl)-indoles, -azaindoles, and -naphthols via the radical addition of xanthate **PS-1** to various olefins followed by radical cyclization.[34] As shown in Scheme 1.35, xanthate **PS-1** can be considered as a convenient source to generate chlorodifluoromethyl radicals which undergo the radical addition cyclization to form adduct **PS-2**. (2, 2-Difluoroethyl)-indole **PS-3** is formed via the elimination of chlorine from **PS-2** by using DBU.



Scheme 1.35 Synthesis of (2, 2-difluoroethyl)-indole **PS-3**

3.3.2. The synthesis of polycyclic aminopyrimidones

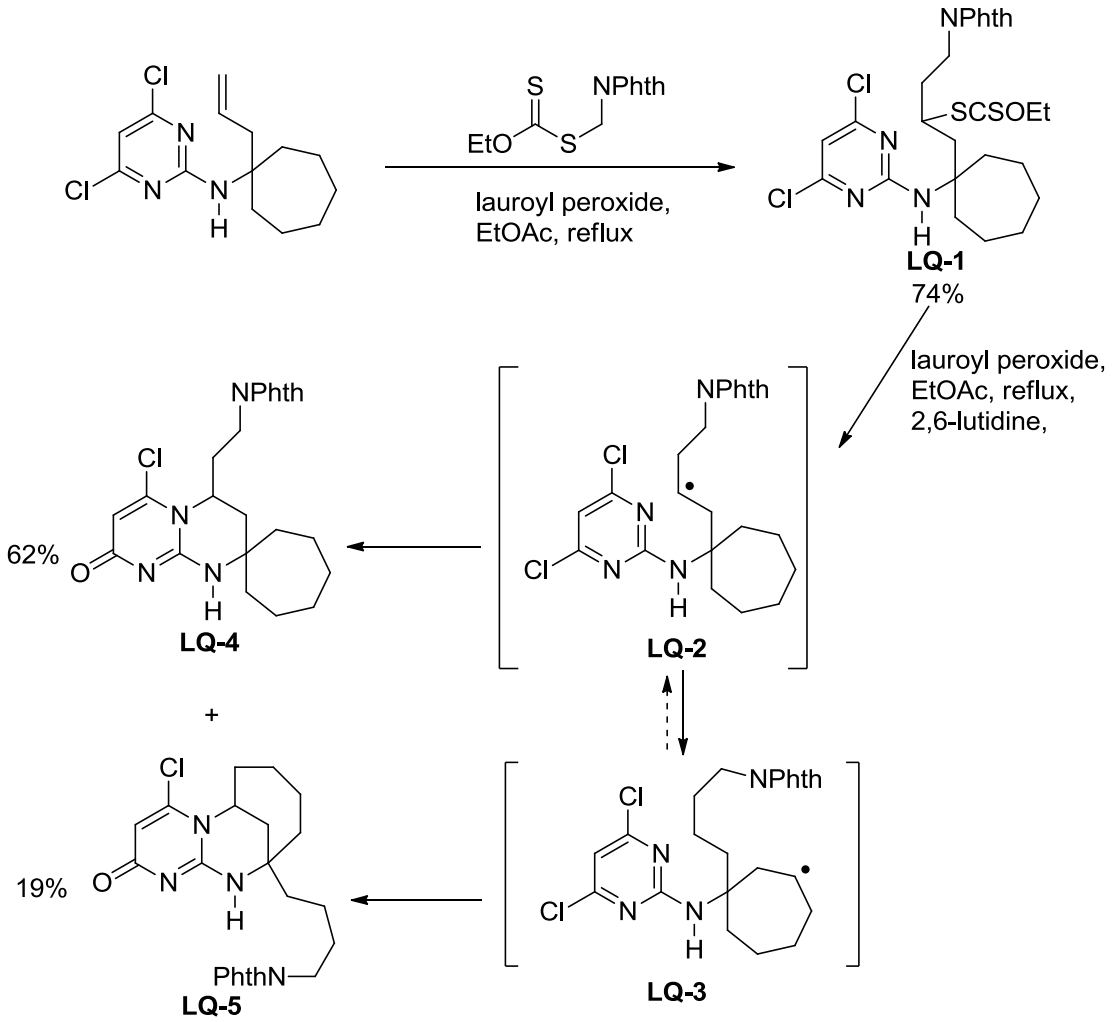
In an ongoing work on the radical cyclization on pyridine and pyrimidine rings,[35] an unexpected observation was recently made. As described in Scheme 1.36, it was found that the cyclization of **LQ-1** gave two different cyclization products, the major being **LQ-4** and the minor **LQ-5.** This represents a synthetically valuable radical ring

[33] (a) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.*, **2001**, *3*, 1069. (b) Li, S.; Zard, S. Z. *Org. Lett.*, **2013**, 15, 5898. (c) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Gagosz, F.; Zard, S. Z. *Org., Lett.* **2003**, 5, 2655. (e) Gagosz, F.; Zard, S. Z. *Org. Synth.* **2007**, 84, 32. (f) Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, 46, 455. (g) Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, 71, 2352.

[34] Salomon, P.; Zard, S. Z. *Org. Lett.*, **2014.** *ASAP.*

[35] (a) El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, *42*, 4422. (b) Laot, Y.; Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784.

closure onto a pyrimidine nitrogen.[36] Radical intermediate **LQ-3** is formed via a 1, 5-hydrogen shift process.



Scheme 1.36 Synthesis of polycyclic aminopyrimidones

4. Radical reactions associated with the xanthates developed in other groups

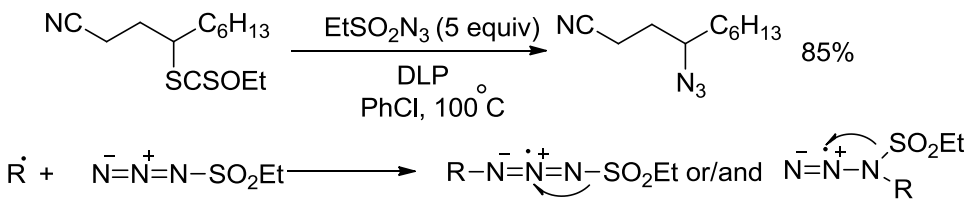
4.1. Radical azidation

In 2000, a radical azidation process was reported by Renaud and co-workers.[37] As illustrated in Scheme 1.37, the R radical generated from the cleavage of the C-S bond in xanthate derivatives was captured by ethanesulfonyl azide to form the

[36] Qin, L.; Liu, Z.; Zard, Z. S. *Org. Lett.*, **2014**, *ASAP.*

[37] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496.

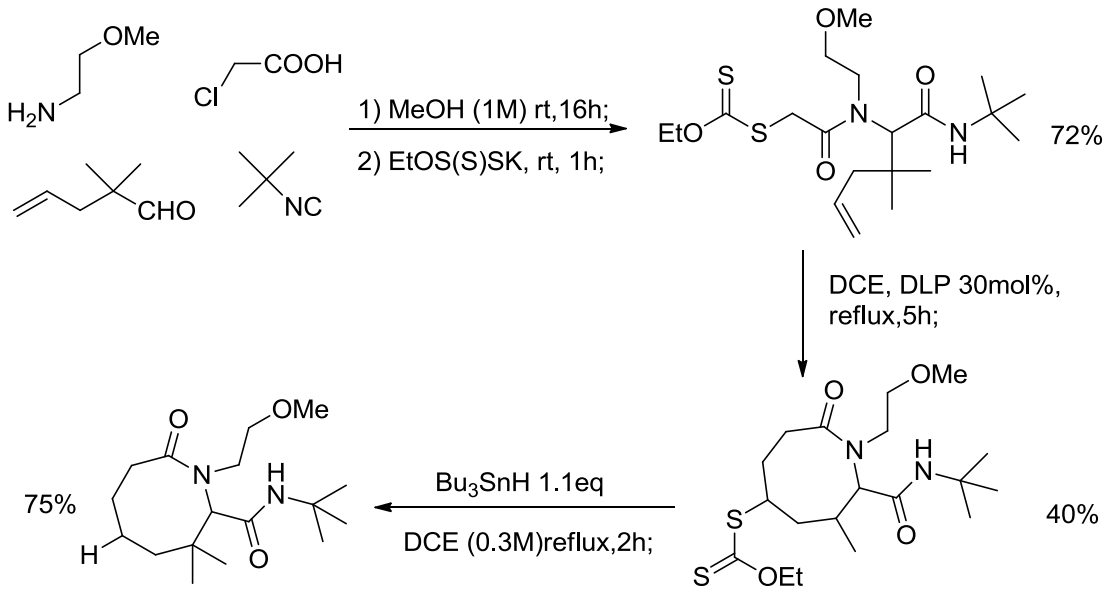
corresponding alkyl azides.



Scheme 1.37 Radical azidation

4.2. Ugi/xanthate cyclization

The Ugi reaction is well known for its rapid combination of multi components in one pot. The combination of Ugi reaction and xanthate radical cyclization onto alkenes was reported by El Ka ïm and co-workers in 2006 (Scheme 1.38).[38] This multi component procedure consists of chloroacetic acid, primary amines, aldehydes and isocyanides, which was then treated with potassium ethyl xanthate to give the xanthate Ugi adducts. Next, the radical cyclization followed reductive elimination of xanthate group afforded the corresponding cyclization product.

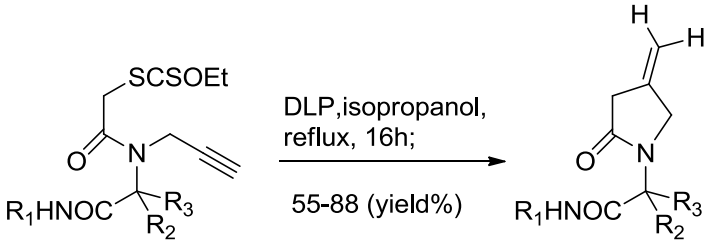


Scheme 1.38 Ugi/xanthate cyclization

[38] El Ka ïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E. *Tetrahedron Lett.* **2006**, *47*, 8259.

4.3. Xanthate-based radical cyclization onto alkynes

Besides the radical addition or cyclization of xanthate to alkenes, even alkynes can be used to undergo the radical reaction with xanthates. Recently, El Kaïm and co-workers reported the radical cyclization of xanthates to alkynes in generally good yield to form lactams.[39] The xanthate was obtained by the same Ugi reaction, but propargylamine was used as one of the components in this Ugi reaction (Scheme 1.39).



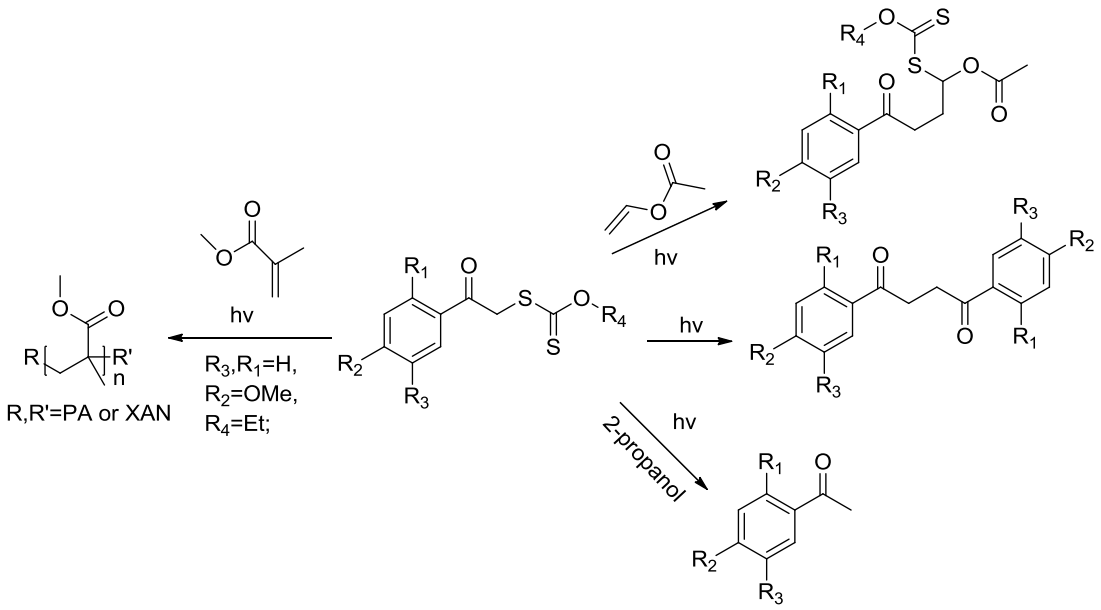
Scheme 1.39 Xanthate-based radical cyclization onto alkynes

4.4. Photoinitiated homolytic scission of C-S bond

Besides lauroyl peroxide, AIBN or other initiators, the homolytic scission of C-S can be accomplished by irradiation in an initiation step. Recently, Klán and co-workers investigated the photochemistry of *S*-phenacyl xanthate.[40] As illustrated in Scheme 1.40, the radical fragments generated via the homolytic scission of C-S could further undergo the radical addition with vinyl acetate or reduction by 2-propanol or polymerization or dimerization.

[39] El Kaïm, L.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M. A.; Perez-Labrada, K. *Chem. Commun.* **2010**, *46*, 2489.

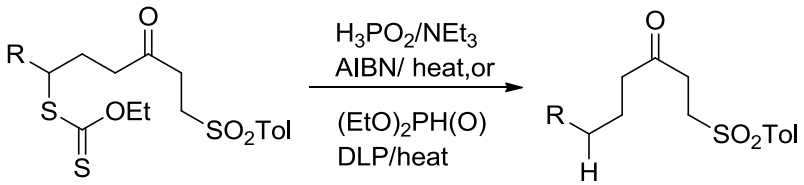
[40] Veetil, A. T.; Šolomek, T.; Ngoy, B. P.; Pavlíková, N.; Heger, D.; Klán, P. *J. Org. Chem.* **2011**, *76*, 8232.



Scheme 1.40 Photoinitiated reactions of *S*-phenacyl xanthate

4.5. Reductive elimination of xanthate groups

There have been numerous studies demonstrating the utility of the xanthate but it is often necessary to remove this group from the resulting adduct. Various tin-free methods for the reductive removal of the xanthate group have been developed in the past few years. One highly efficient procedure to reduce the xanthate group was applied by Boivin and co-workers in 2003 using a procedure described initially by Barton (Scheme 1.41).[41] This process employs a combination of hypophosphorous acid and triethylamine to accomplish the radical reductive dexanthylation in generally high yield.



Scheme 1.41 Reductive elimination of xanthate group by using hypophosphorous acid and triethylamine

[41] (a) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, T. V. *Org. Lett.* **2003**, *5*, 1645. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (c) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838. (d) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 2311-2314. (e) Barton, D. H. R.; Parekh S. I.; Tse, C.-L. *Tetrahedron Lett.* **1993**, *34*, 2733.

Conclusion

In this chapter, we have presented in general terms radical reactions associated with the thiocarbonyl group. The Barton decarboxylation and the Barton-McCombie deoxygenation are two of the most powerful radical reactions that were briefly introduced along with their later improvements. The degenerative transfer addition of xanthates to alkenes developed largely in our group has demonstrated its highly valuable potential for organic synthesis. This opens up vast possibilities to rapidly assemble complex structures. Various functional groups can be incorporated into the final products, either through the xanthate partner or through the alkene.

Chapter 2

Synthesis of Amines via Ionic or Radical Methods

Introduction

Amines as fundamental species or moieties are ubiquitous in natural products or pharmaceutical compounds. For instance, chlorpromazine is a dopamine antagonist of the typical antipsychotic class of medications possessing additional antiadrenergic, antiserotonergic, anticholinergic and antihistaminergic properties used to treat schizophrenia; chlorpheniramine (brand name: Chlorphen-12), as a first-generation alkylamine antihistamine is used to prevent the symptoms of allergic conditions such as rhinitis and urticarial. Alkaloids, a vast family of natural products, contain by definition at least one basic nitrogen. Swainsonine, an indolizidine alkaloid, is a potent inhibitor of Golgi α-mannosidase II, an immunomodulator, and a potential chemotherapy drug; recently, Igarashi and co-workers reported a new pyrrolidine alkaloid, preussin B, that was isolated from the culture extract of the fungus *Simplicillium lanosoniveum* TAMA 173 (Figure 2.1).

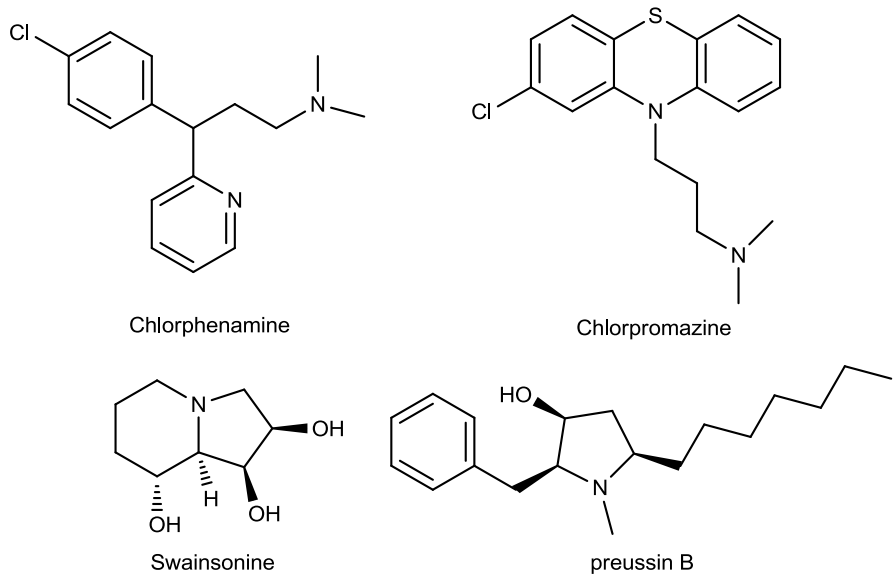
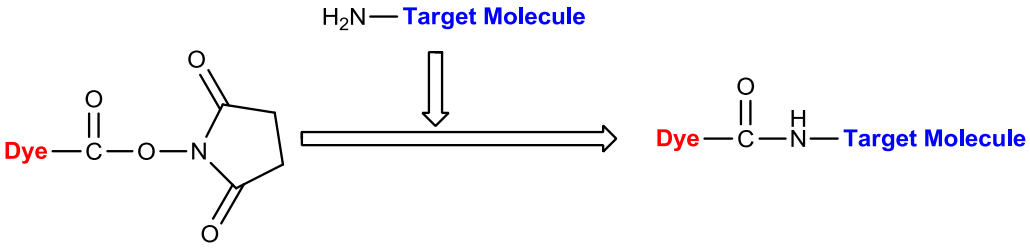


Figure 2.1 Examples of biologically active compounds containing amino-unit

In material science amines as starting materials are involved in the design of amine-reactive fluorescent dyes used to prepare bioconjugates for immunochemistry, fluorescence *in situ* hybridization (FISH), cell tracing, receptor labeling and

fluorescent analog cytochemistry. As illustrated in Scheme 2.1, there have been a large number of fluorescent amino-reactive dyes used to label various biomolecules.



Scheme 2.1 Label of biomolecules by fluorescent amino-reactive dye

While numerous methods for the preparation of functionalized amine have been reported over the decades, there is still a strong demand for new flexible routes to access complex amine derivatives. An observation made in our group demonstrated that a carbon radical can be stabilized by a phthalimido group, and thus the efficient intermolecular radical chain additions of phthalimido-substituted xanthates to various alkenes could be accomplished. As a result, we were encouraged us to apply this protocol in developing a more practical and general route to highly functionalized amines. In this chapter, our previous work on the preparation of phthalimido-substituted xanthates and xanthates containing other nitrogen group together with their applications in synthesis of functionalized amines will be briefly discussed.

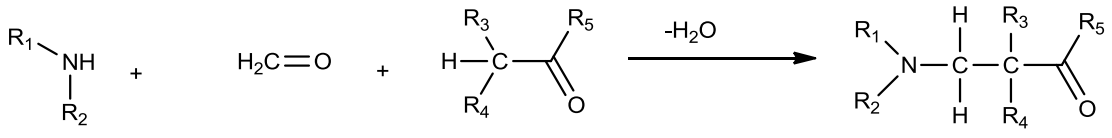
I. Amines synthesis

1. Named reactions in amine synthesis

Numerous classical named reactions are known for the synthesis of amines, such as the Mannich reaction, the Strecker Reaction, the Kabachnik-Fields reaction, the Buchwald-Hartwig cross-coupling, the Petasis boronic acid-Mannich Reaction, the Gabriel synthesis, the Delépine reaction, the Eschweiler-Clarke reaction, the Schmidt reaction, the Curtius rearrangement, the Sharpless asymmetric aminohydroxylation, and the Staudinger ketene cycloaddition.

1.1. The Mannich reaction

In 1903, Tollens and von Marle found that the reaction of acetophenone with formaldehyde and ammonium chloride resulted in the formation of a tertiary amine. Fourteen years later, Mannich studied the generality of this reaction.[42] The Mannich reaction can be considered as the addition a CH-activated compounds to iminium salts or imines which lead to the formation of a substituted β-amino-carbonyl compound known as a Mannich base (Scheme 2.2).[43] Nowadays, the Mannich-Reaction is widely applied in the synthesis of peptides, nucleotides, alkaloids and other amine related compounds.

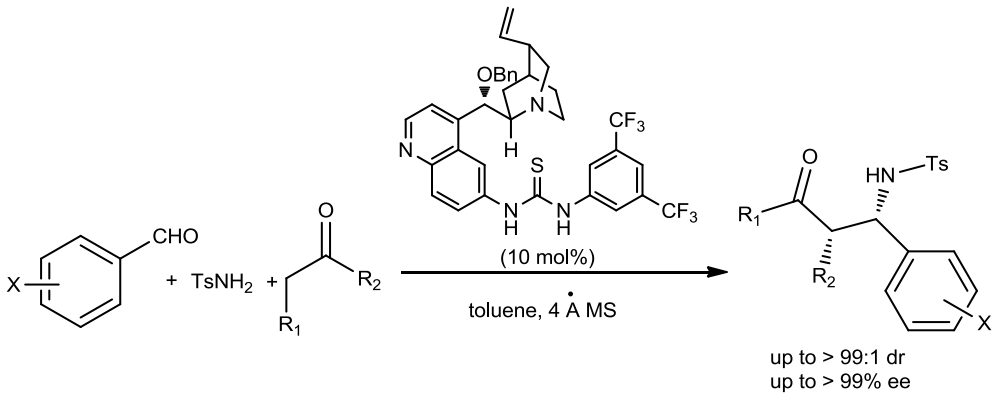


Scheme 2.2 Mannich reaction

Recently, Zhao and co-workers developed a highly enantioselective

[42] Mannich, C.; Krösche, W. *Arch. Pharm. Pharm. Med. Chem.* **1912**, *250*, 647.
[43] Cummings, T. F.; Shelton, J. R., *J. Org. Chem.* **1960**, *25*, 419.

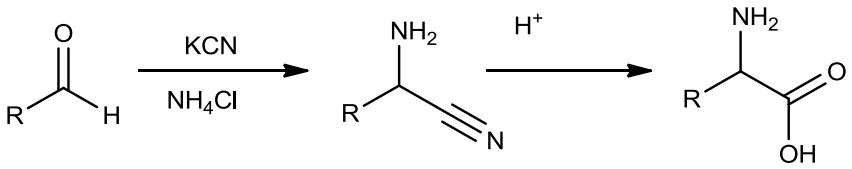
three-components directed Mannich reaction of unfunctionalized ketones.[44] As shown in Scheme 2.3, this multicomponent Mannich reaction consists of an aromatic aldehyde, *p*-toluenesulfonamide, and an unfunctionalized ketone. It was the first time a bifunctional quinidine thiourea was used as a Bronsted base catalyst to accomplish a highly diastereoselective and enantioselective Mannich reaction.



Scheme 2.3 Bronsted base catalyzed Mannich reaction

1.2. The Strecker Reaction

In 1850, A. Strecker devised the first laboratory method to access α-amino acids. The condensation of an aldehyde with ammonium chloride in the presence of cyanide generates an α-aminonitrile and hydrolysis finishes the desired α-amino-acid (Scheme 2.4).[45] The development of the Strecker reaction allows the use of ammonia, primary, or secondary amines and both ketones and aldehydes as substrates. The Strecker reaction has proved to be a powerful tool for the synthesis of amino acids.

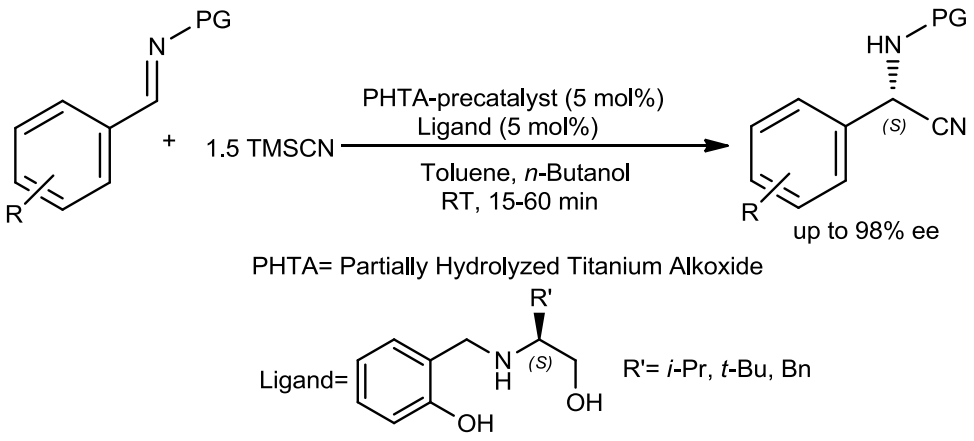


Scheme 2.4 Strecker reaction

[44] Guo, Q.; Zhao, J. C.-G. *Org. Lett.*, **2013**, *15*, 508.

[45] (a) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27. (b) Strecker, A. *Ann. Chem. Pharm.* **1854**, *91*, 349.

However, the enantioselective synthesis of aminonitriles remains a quite challenging issue. A highly enantioselective titanium-catalyzed cyanation of imines at room temperature was recently described by Chai and co-workers (Scheme 2.5).[46] The reaction of various *N*-protected imines with TMSCN was catalyzed by a partially hydrolyzed titanium alkoxide precatalyst together with a readily available *N*-salicyl-*β*-aminoalcohol ligand to form the corresponding aminonitrile with high enantioselectivity.



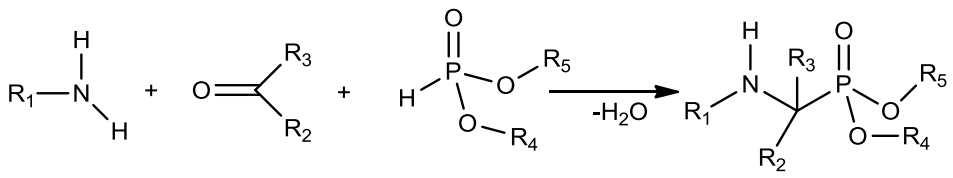
Scheme 2.5 Titanium-catalyzed Strecker reaction

1.3. The Kabachnik-Fields reaction

This multi-component reaction was concurrently reported by Kabachnik and Fields in 1952 (Scheme 2.6). This one pot process involves the reaction of amines, carbonyl compounds and dialkyl phosphonates to form α-amino phosphonates and their derivatives, which are useful as chelating agents.[47]

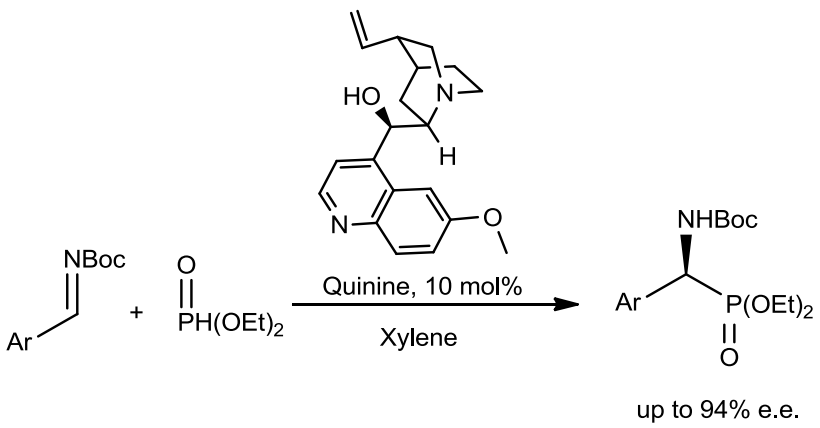
[46] Seayad, A. M.; Ramalingam, B.; Yushinaga, K.; Nagata, T.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 264.

[47] (a) Kabachnik, M.I.; Medved, T.Y. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689. (b) Fields, E.K. *J.Am. Chem. Soc*. **1952**, *74*, 1528.



Scheme 2.6 Kabachnik-Fields reaction

A recent study of the organocatalytic asymmetric hydrophosphonylation of imines by Ricci and co-workers resulted in the synthesis of enantiomerically enriched *α*-amino phosphonic acid derivatives in a simple and efficient manner (Scheme 2.7).[48] The readily available quinine (10 mol%) as the catalyst for the addition of diethyl phosphate to *N*-Boc protected imines ensured the high enantioselectivity.



Scheme 2.7 Organocatalytic asymmetric hydrophosphonylation of imines

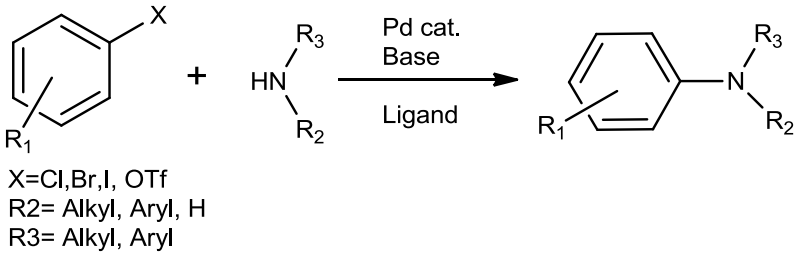
1.4. The Buchwald-Hartwig Cross-Coupling

C-N bond formation via palladium-catalyzed cross-coupling of aryl halides or trifluoromethanesulfonates with amines in the presence of base is known as the Buchwald-Harwig cross-coupling (Scheme 2.8).[49] Between 1994 and the late 2000s Buchwald and Hartwig established the scope of this aromatic C-N bond formation.

[48] Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.*, **2006**, *71*, 6269.

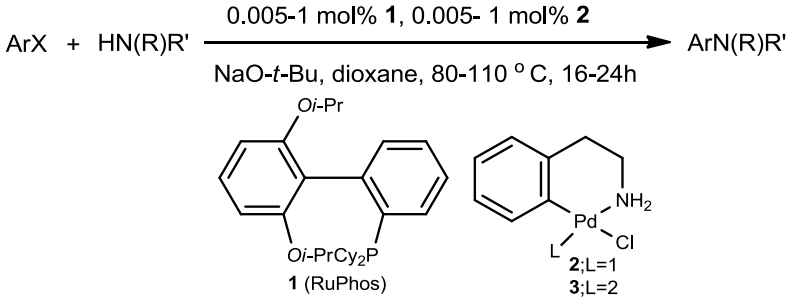
[49] (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

Indeed, the Buchwald-Harwig cross-coupling has been widely applied for the formation of aryl C-N bonds in the synthesis of pharmaceuticals and natural products.



Scheme 2.8 Buchwald-Hartwig cross-coupling

Recently, a multiligand based Pd catalyst for the C−N cross-coupling reaction was investigated by Buchwald and co-workers (Scheme 2.9). This Pd catalyst system was based on two biarylphosphine ligands, which demonstrated that two ligands together could display higher reactivity than either of them exhibited separately.[50] This multiligand based Pd catalyst system opens up an interesting approach for catalyst development.



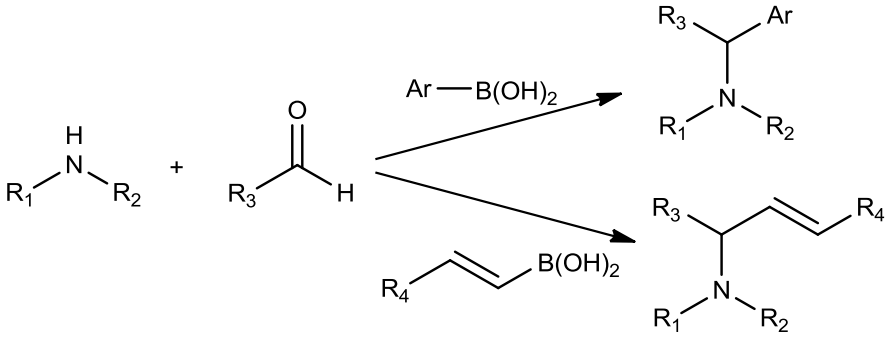
Scheme 2.9 Multiligand based Pd catalyst system

1.5. The Petasis Boronic Acid-Mannich reaction

In 1993, Petasis and co-workers reported a practical way towards the synthesis of allylic amines or amino-acids which may be considered as a variation of Mannich

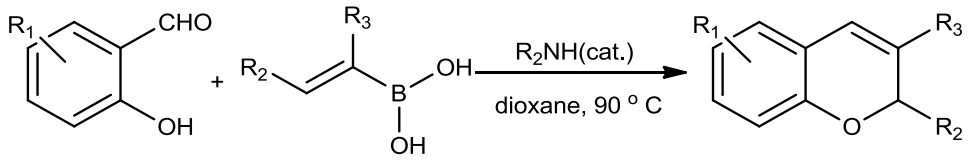
[50] Fors, B. P., Buchwald, S. L. *J. Am. Chem. Soc.*, **2010**, *132*, 15914.

reaction (Scheme 2.10).[51] In this multicomponent reaction, the boronic acid serves as the nucleophile and plays the same role as the enolizable ketone component in the Mannich reaction.



Scheme 2.10 Petasis Boronic Acid-Mannich Reaction

One application of the Petasis reaction for the synthesis of 2*H*-chromenes was studied by Finn and co-workers (Scheme 2.11).[52] Vinylic or aromatic boronic acids, o-phenolic aldehydes, and amines together underwent condensation and cyclization to form highly diverse 2*H*-chromenes. It appears that the successful condensation is assisted by the hydroxyl group adjacent to the aldehyde moiety.



Scheme 2.11 Synthesis of 2*H*-chromenes

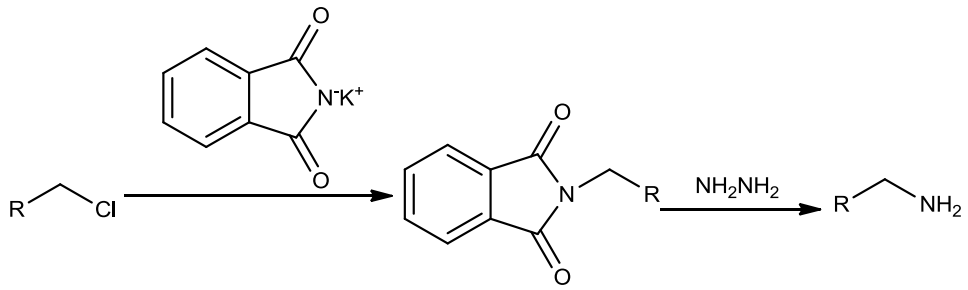
1.6. The Gabriel synthesis

The use of potassium phthalimide as the nitrogen source and nucleophile to react with alkyl halides was initially described in 1884, but later, in 1887, Gabriel studied

[51] (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett*. **1993**, *34*, 583–586. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1997**, *119*, 445–446. (c) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 11798.

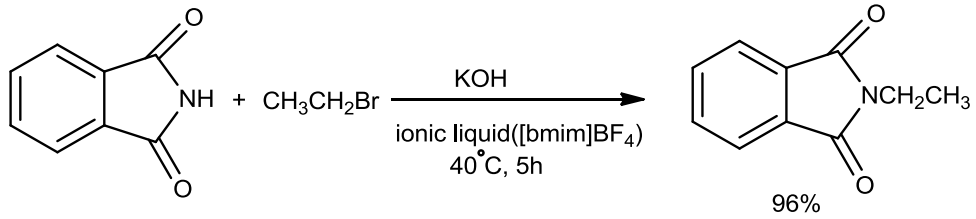
[52] Wang, Q.; Finn, M. G. *Org. Lett.*, **2000**, *2*, 4063.

the generality of this process (Scheme 2.12).[53] Various primary amines can be easily obtained from the corresponding alkyl halides by a simple two steps sequence.



Scheme 2.12 Gabriel synthesis

Chen and co-workers proposed a modification of the Gabriel synthesis (Scheme 2.13). The alkylation of the phthalimide is done in ionic liquids such as [bmim] BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate) by using potassium hydroxide as the base.[54] Lower reaction temperatures, higher yields and reaction rates were achieved by using ionic liquids as the solvent.



Scheme 2.13 Gabriel synthesis in ionic liquids

The use of azide as the nucleophile is also a convenient route to amines, especially in small scale work. The azide group is then easily converted into an amine by various reducing agents.

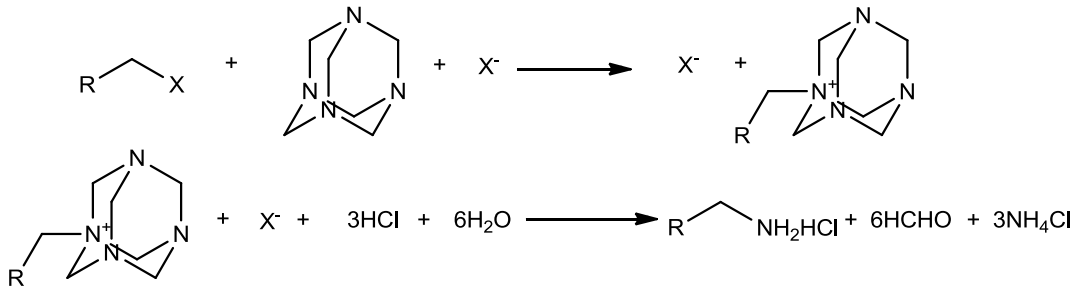
1.7. Delépine reaction

In 1895, the French chemist Delépine initially reported this practical way to

[53] Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224.

[54] Le, Z.; Chen, Z.; Hu, Y.; Zheng, Q. *Synthesis*, **2004**, 208.

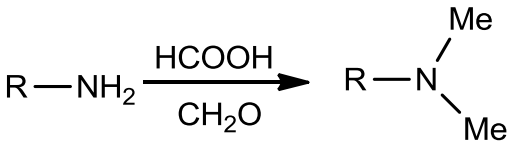
access primary amines (Scheme 2.14). Compared with the Gabriel synthesis, the Delépine reaction introduces an amino unit by using urotropine, which also behaves like an amine nucleophile. The hydrolysis of the quaternary ammonium salt was assisted by acid.[55]



Scheme 2.14 Delépine reaction

1.8. The Eschweiler-Clarke reaction

Since Leuckart reported the first reductive alkylation of an amine in 1885, Eschweiler and Clarke found that formaldehyde could introduce a methyl group to a primary or a secondary amine to furnish the corresponding tertiary amine in one-pot, which is essentially an amine methylation process (Scheme 2.15).[56]



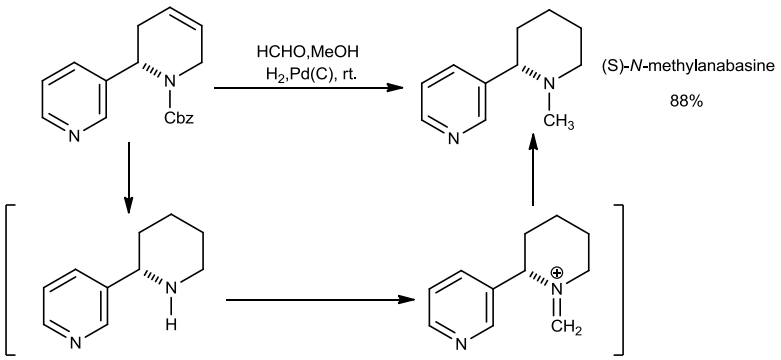
Scheme 2.15 Eschweiler-Clarke reaction

During the enantioselective total syntheses of several piperidine and pyrrolidine alkaloids involving an Eschweiler-Clarke reaction, Lebreton and co-workers completed the total synthesis of (S)-*N*-methylanabasine at room temperature in high

[55] Brandänge, S.; Rodriquez, B. *Synthesis*, **1988**, 347-348.

[56] (a) Eschweiler, W. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 880. (b) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571. (c) Moore, M. L. *Org. React.* **1949**, *5*, 301. (d) Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829.

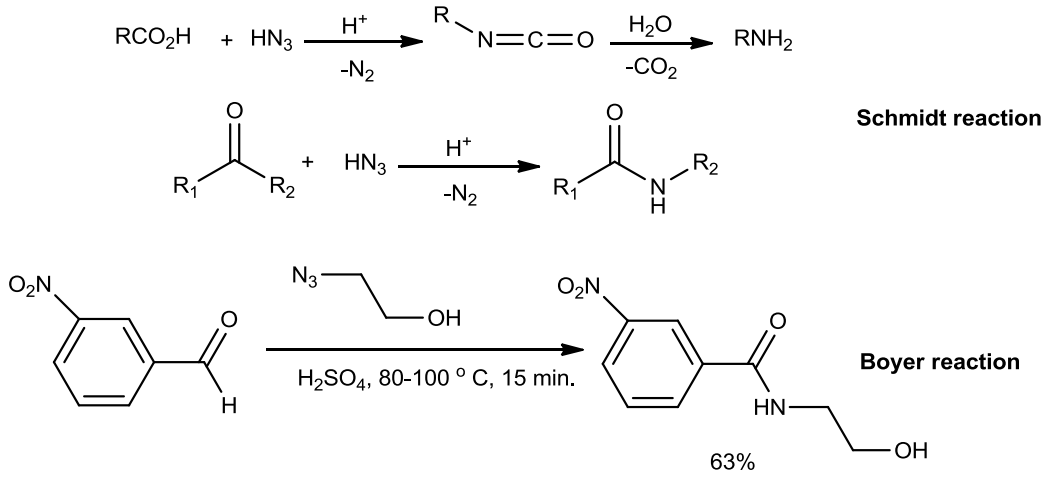
yield (Scheme 2.16).[57]



Scheme 2.16 Synthesis of (S)-*N*-methylanabasine

1.9. The Schmidt reaction

In 1923, Schmidt found a C-to N alkyl migration in an acyl azide with the loss of nitrogen (Scheme 2.17). Unlike the related Curtius and Hoffmann rearrangements, this reaction is completed in one single step from carboxylic acids.[58] Later in 1955, Boyer extended the scope of this reaction by using alkyl azides.[59]



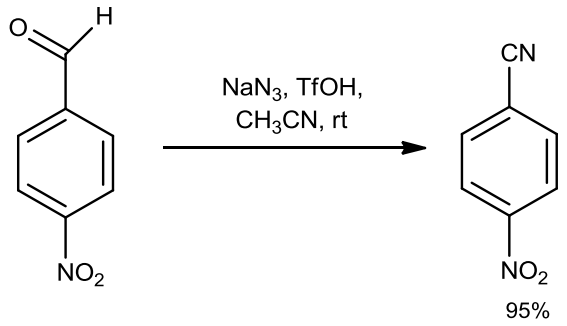
Scheme 2.17 Schmidt reaction

[57] Felpin, F. X.; Girard, S.; Vo-Thanh, G.; Robins, R.J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.

[58] (a) Schmidt, K. F. Z. *Angew. Chem.* **1923**, *36*, 511. (b) Schmidt, K. F. *Ber. dtsch. Chem. Ges.* **1924**, *57*, 704.

[59] Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951.

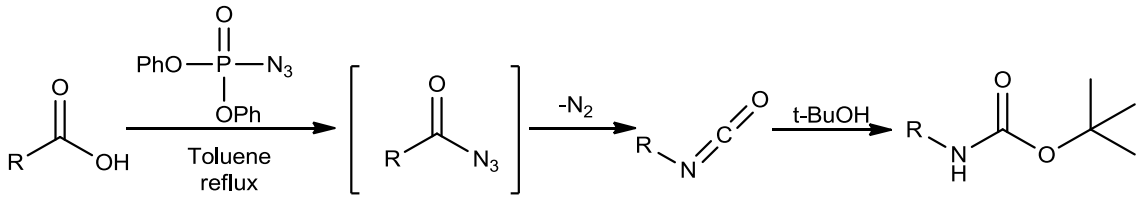
The Schmidt reaction of aldehydes results in the formation of mixtures of the corresponding formanilides and nitriles, and this remains a problem. Recently, a chemoselective Schmidt reaction mediated by trifluoromethanesulfonic acid converts aldehydes into nitriles as the sole products and is described by Prabhu and co-workers (Scheme 2.18).[60]



Scheme 2.18 Schmidt reaction mediated by trifluoromethanesulfonic acid

1.10. The Curtius rearrangement

The rearrangement of an acyl azide to an isocyanate was first discovered by Curtius in 1890 and is now known as the Curtius rearrangement (Scheme 2.19).[61] Following loss of nitrogen, the isocyanate intermediate can be trapped by different nucleophiles such as water, amines or alcohols. In the case of water as the nucleophile, a primary amine can be obtained. The Curtius rearrangement has found wide application in organic synthesis, especially in the total synthesis of natural products.



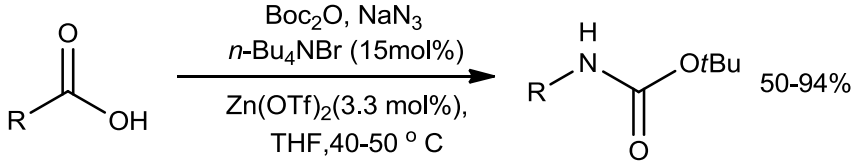
Scheme 2.19 Curtius rearrangement

A mild and efficient one pot Curtius rearrangement was reported by Leogane and

[60] Rokade, B. V., Prabhu, J. R., *J. Org. Chem.*, **2012**, *77*, 5364-5370.

[61] (a) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) Curtius, T. *J. Prakt. Chem.* **1894**, *50*, 275.

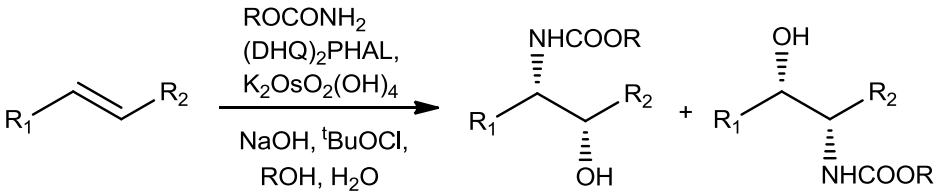
co-workers (Scheme 2.20).[62] Instead of diphenylphosphorazidate, they used sodium azide to work with di-*tert*-butyl dicarbonate and carboxylic acid to form the acyl azide intermediate followed by the assistance of tetrabutylammonium bromide and zinc (II) triflate to provide the *N*-Boc-protected amines.



Scheme 2.20 Curtius rearrangement by using sodium azide

1.11. The Sharpless asymmetric aminohydroxylation

The transformation of simple alkenes into protected amino alcohols in an enantioselective manner was reported by Sharpless et al. in 1996. It is now known as the Sharpless asymmetric aminohydroxylation (Scheme 2.21).[63] Since *β*-amino alcohols are important fragments in many biologically interesting compounds, this method has found application in the development of pharmaceutical libraries and in the stereocontrolled total synthesis of natural products.



Scheme 2.21 Sharpless asymmetric aminohydroxylation

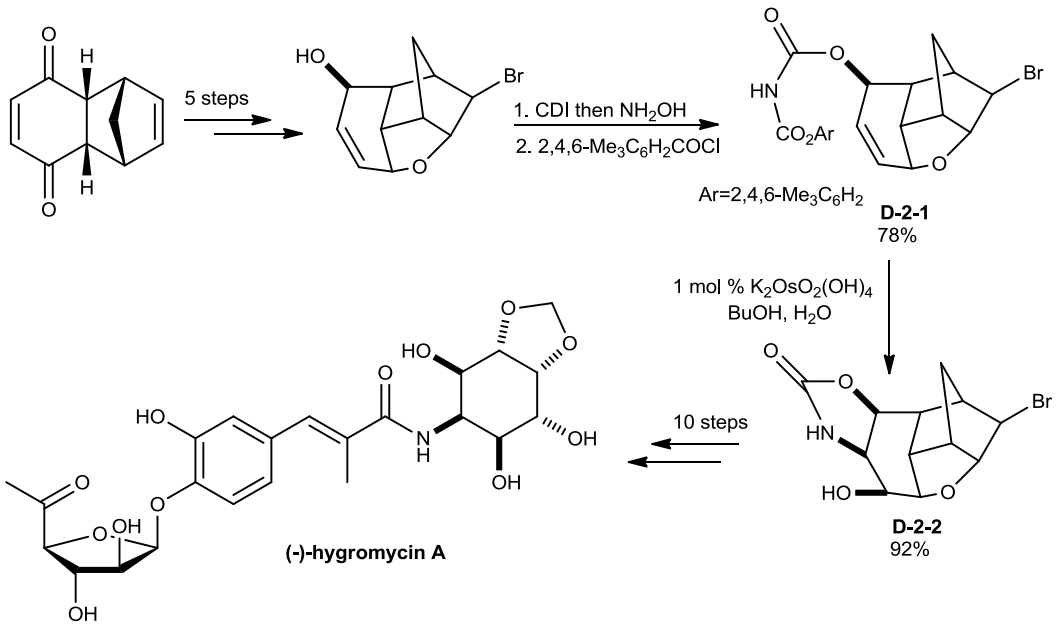
Thus, during the total synthesis of (-)-hygromycin A, Donohoe and co-workers accomplished the transformation of **D-2-1** into **D-2-2** via a Sharpless asymmetric aminohydroxylation (Scheme 2.22).[64] In the presence of catalytic amount of

[62] Lebel, H.; Leogane, O. *Org. Lett.*, **2005**, *7*, 4107.

[63] (a) Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *36*, 1483. (b) Mcleod, M. D.; Bodkin, J. A. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 2733.

[64] Donohoe, T. J.; Flores, A.; Bataille, C. J. R.; Churruca, F. *Angew. Chem. Int. Ed.* **2009**, *121*,

potassium osmate (1 mol %), **D-2-1** was converted into **D-2-2** in aqueous butanol at room temperature in high yield.



Scheme 2.22 Total synthesis of (-)-hygromycin A

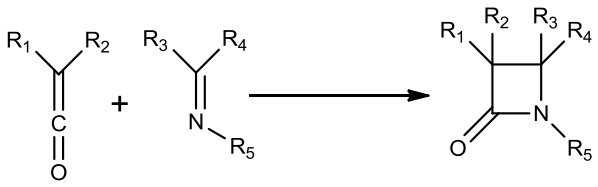
1.12. The Staudinger ketene cycloaddition

β-Lactams can be formed by a formal [2+2]-cycloaddition of imines to ketenes, and this transformation was initially reported by Staudinger in 1907. Either the ketene or the imine can act as the nucleophile or the electrophile in this reaction (Scheme 2.23). [65] Besides imines, compounds such as alkenes, ketones, acetylenes, thiocarbonyls, isocyanates, carbodiimides, *N*-sulfinylamines, nitroso- and azo-derivatives can also react with ketenes to form four-membered ring derivatives.[66]

6629.

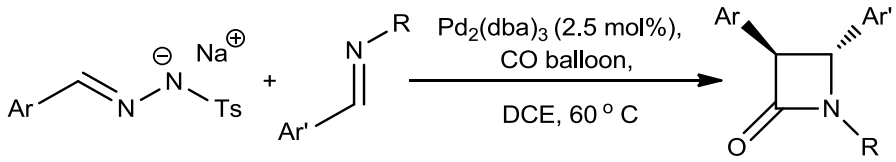
[65] Staudinger, H. *Ber*. **1907**, *40*, 1145.

[66] (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.*, **2002**, *124*, 1578. (b) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.



Scheme 2.23 Staudinger ketene cycloaddition

Recently, a new Pd-catalyzed tandem carbonylation-Staudinger cycloaddtion method was established by Wang and co-workers (Scheme 2.24).[67] The ketene intermediate was formed by heating *α*-diazo-carbonyl compounds or *N*-tosylhydrazone salts in the presence of a palladium catalyst and CO. Then various nucleophiles underwent the cycloaddition with the ketene intermediates to give *β*-lactam derivatives with excellent *trans* diastereoselectivity.



Scheme 2.24 Pd-Catalyzed tandem carbonylation-Staudinger cycloaddtion

2. The hydroaminomethylation of alkenes

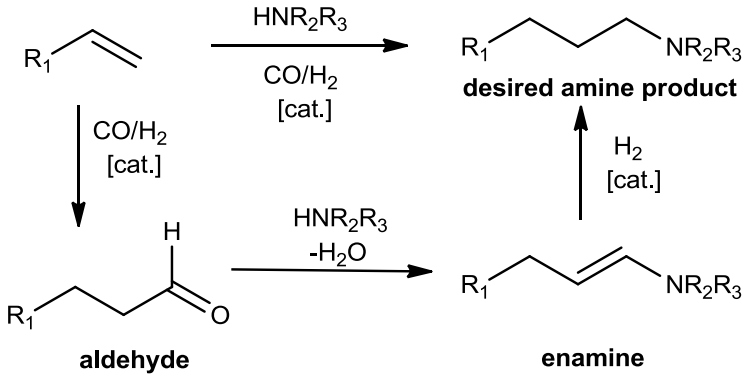
Although both the hydroamination and the hydrocyanation of alkenes have atom efficiencies of 100%, their application in industrial processes for the production of amines usually results in large amounts of waste, together with other problems. In contrast, the hydroaminomethylation of alkenes as an alternative method, initially reported by Reppe in 1949 at BASF, has a greater potential for commercial application.[68]

As described in Scheme 2.25, the hydroaminomethylation of alkenes is usually a one-pot cascade reaction consisting in a hydroformylation and a reductive amination

[67] Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

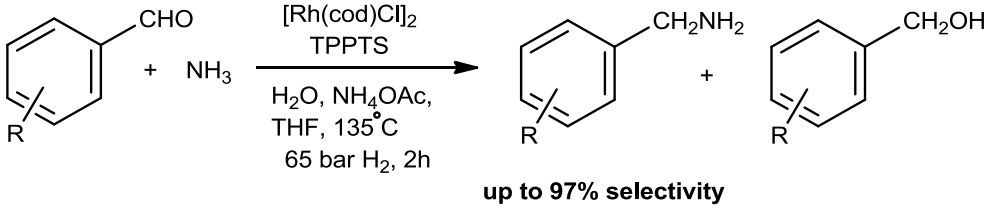
[68] (a) Reppe, W.; Vetter, H. *Liebigs Ann. Chem.* **1953**, *582*, 133. (b) Reppe, W. *Experientia* **1949**, *5*, 93. (c) Crozet, D.; Urrutigoity, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102.

to produce the desired amine. In this reaction, primary and secondary amines can be used as the nitrogen sources; however, due to the higher nucleophilicity of primary amines compared to ammonia, the direct use of ammonia in hydroaminomethylation to produce primary amines is still a quite challenging task.



Scheme 2.25 Hydroaminomethylation of alkenes

The first examples of a reductive amination with ammonia were reported by Beller and co-workers in the early 2000s (Scheme 2.26).[69] In a biphasic system the transformation of benzaldehydes to benzylamines was achieved by using an Rh-catalyst together with water-soluble phosphine and ammonium acetate. The high yield and up to 97% selectivity of this reaction made it extremely powerful to produce benzylamines.



TPPTS= tri sodium salt of meta trisulfonated triphenylphosphine

Scheme 2.26 Reductive amination of benzaldehyde using a Rh-catalyzed process

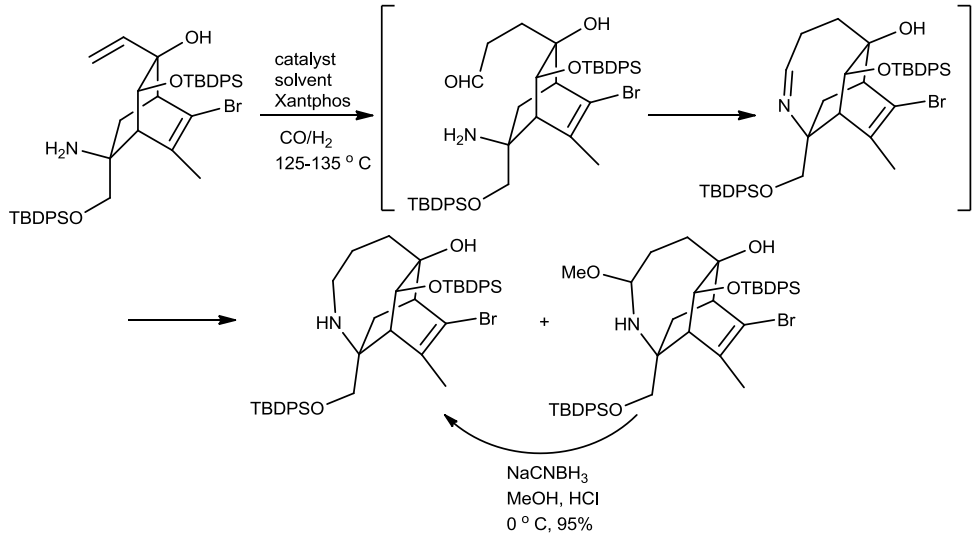
Recent improvements of the hydroaminomethylation of alkenes by the design of efficient metal catalysts open numerous opportunities for the synthesis of amines,

[69] Gross, T.; Seayad, A.M.; Ahmed, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055.

which will emerge in the future.

2.1. Intramolecular hydroaminomethylation of alkenes

The intramolecular hydroaminomethylation has gained importance for the building of nitrogen-containing heterocycles, such as pyrrolidines, piperidines and azepines.[70] As illustrated in Scheme 2.27, during the synthesis of the lycopladine H, Weinreb and co-workers constructed an eight membered azocane ring via an intramolecular hydroaminomethylation.[71]



Scheme 2.27 Synthesis of the lycopladine H

2.2. Hydroaminomethylation of alkenes based on rhodium-catalyzed process

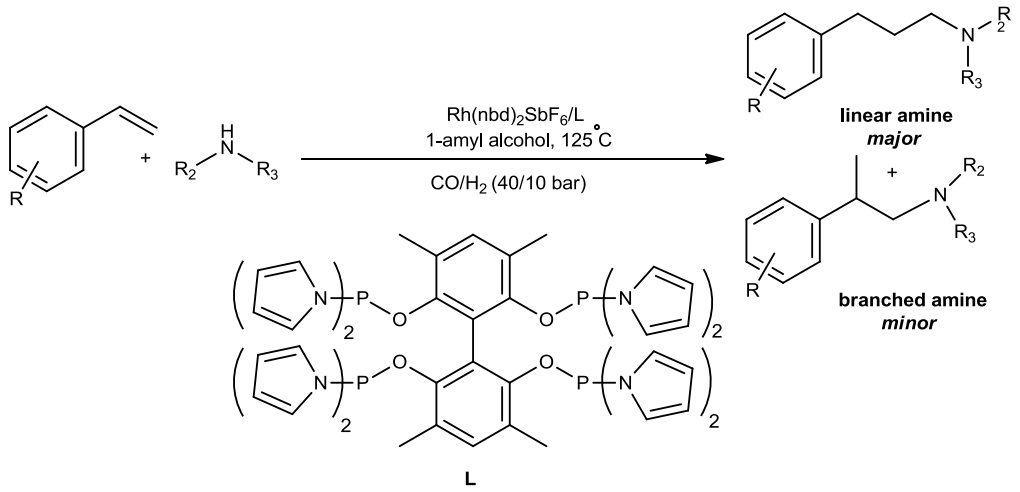
Due to the intrinsic tendency to form the branched amines, the selectivity between the linear and branched amines in hydroaminomethylations, especially for hydroaminomethylation of styrenes, remains challenging.[72] Recently, an efficient,

[70] (a) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (b)Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

[71] Sacher, J. R.; Weinreb, S. M. *Org. Lett.* **2012**, *14*, 2172.

[72] (a) Lin, Y.-S.; Ali, B. E.; Alper, H. *Tetrahedron Lett.* 2001, *42*, 2423. (b) Kostas, I. D. *J. Chem. Res. (S)* **1999**, 630. (c) Kostas, I. D.; Screttas, C. G. *J. Organomet. Chem.* **1999**, *585*, 1. (d) Seayad, A. M.; Selvakumar, K.; Ahmed, M.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 1679. (e) Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 7401. (f) Sun, Y.; Ahmed,

highly linear-selective hydroaminomethylation (*l/b* up to >99:1) of styrenes involving in $Rh(nbd)_2SbF_6$ together with a pyrrole-based 3,3',5,5'-substituted tetraphosphorus ligand as the catalyst was reported by Zhang and co-workers. This is so far the highest liner selectivity observed (Scheme 2.28).[73]



Scheme 2.28 Linear selective hydroaminomethylation of styrenes

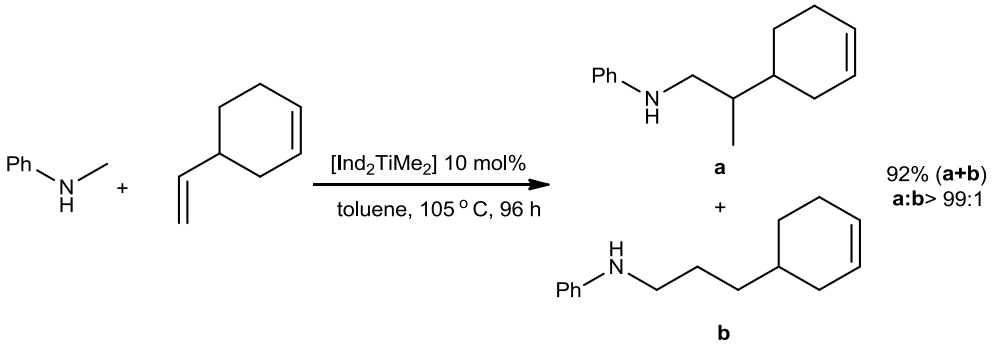
2.3. Hydroaminomethylation of alkenes based on titanium-catalyzed process

Traditionally, the hydroaminomethylation of alkenes was mainly based on Rhodium catalyzed processes. Recently, Doye and co-workers reported an efficient hydroaminomethylation of alkenes based on titanium catalysts to achieve a high branched amine selectivity at low temperature (Scheme 2.29).[74] For example, the reaction of 4-vinylcyclohex-1-ene with *N*-methylaniline can be mediated by a catalytic amount of Ind_2TiMe_2 and provides a regioselectivity > 99:1 at 80 ℃ within 24h.

M.; Jackstell, R.; Beller, M.; Thiel, W. R. *Organometallics* **2004**, *23*, 5260.

[73] Li, S., Huang, K., Zhang, J., Wu, W., Zhang, X. *Org. Lett*. **2013**, *15*, 3078.

[74] Kubiak, R., Prochnow, I., Doye, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 2626.

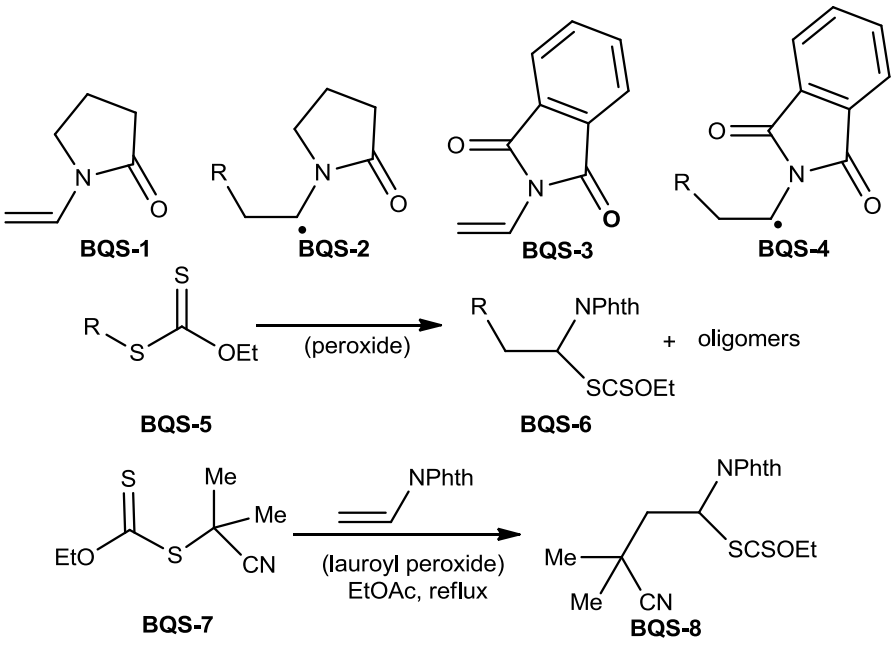


Scheme 2.29 Titanium catalyzed hydroaminomethylation of alkenes

II Applications of xanthate chemistry in amine synthesis

1. *S*-phthalimidomethyl xanthate

An interesting observation was disclosed by our group: the radical addition of *N*-vinyl phthalimide **BQS-3** with many xanthates formed mostly oligomers other than the desired adducts **BQS-6**, in contrast to *N*-vinyl pyrrolidone **BQS-1** which underwent generally an efficient addition (Scheme 2.30). Only the addition of *N*-vinyl phthalimide with **BQS-7** could secure a good yield of **BQS-8** under usual conditions. From these results, it appears that adduct radical **BQS-4** was more stable than adduct radical **BQS-2**. At first glance comparing **BQS-4** and **BQS-2,** one might consider the electron density on the nitrogen of **BQS-2** to be higher than that of **BQS-4**. Therefore, an investigation was undertaken by our group to further explore this unanticipated observation.[75]

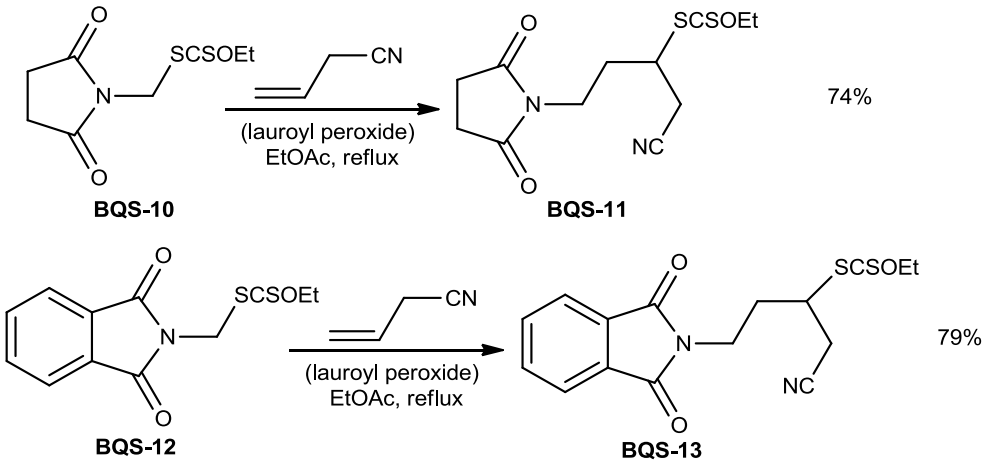


Scheme 2.30 Addition of xanthate to *N*-vinyl phthalimide

The results shown in Scheme 2.31 demonstrated that the aromatic ring had only a

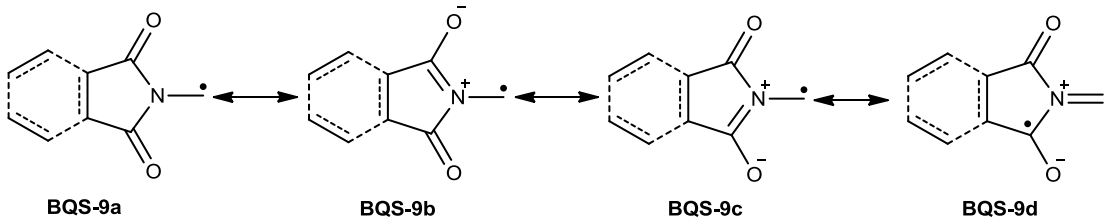
[75] Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279.

limited effect on the efficiency of the process, which turned our attention to the effect of the second carbonyl group.



Scheme 2.31 Addition of xanthate **BQS-10** and **BQS-12** to allyl cyanide

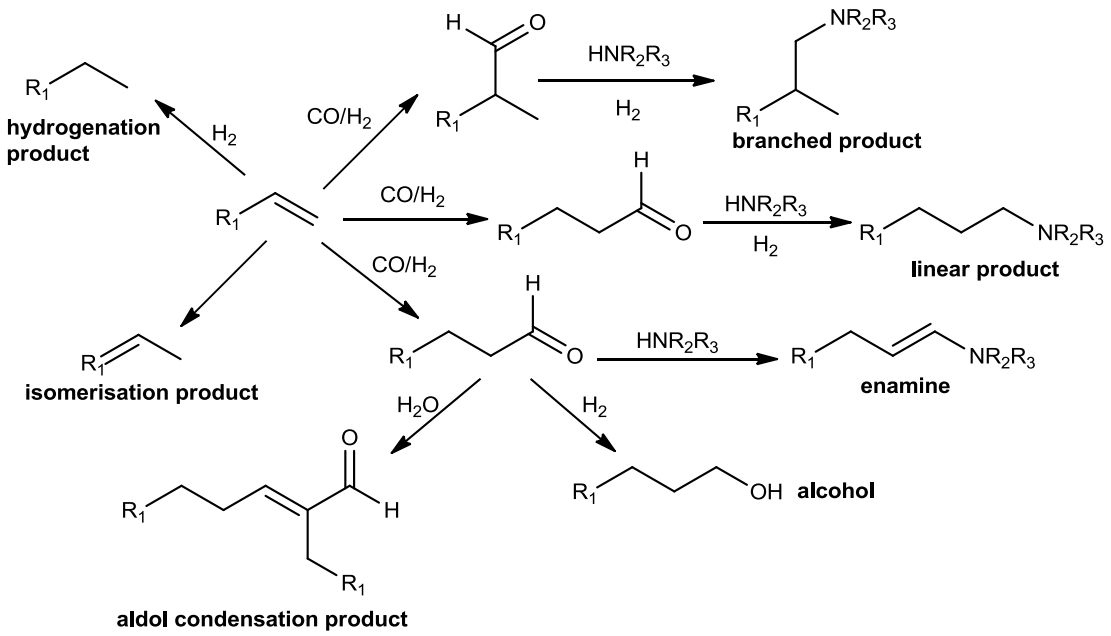
By closely studying the resonance structures of radical intermediate **BQS-9** (Scheme 2.32), the structures of contributors **9b**, **9c** and **9d** where the radical appears to benefit some allylic character, can give us a plausible explanation: the more extended delocalization has small but sufficient stabilizing effect on radical **BQS-9** to allow the formation of the desired products instead of unwanted oligomers.



Scheme 2.32 Resonance structures of radical intermediate **BQS-9**

Hydroaminomethylation, as a powerful tool for the synthesis of amines, was introduced in the previous paragraph. However, because the higher nucleophilic property of the primary amine product towards the aldehyde generated in the hydroformylation step, undesired amine products are observed in hydroaminomethylation with ammonia. Furthermore the lack of selectivity between

linear and branched products as shown in Scheme 2.33 along with all other possible side reactions may lead to unsurmountable complexity.[76] These drawbacks make the chemical amino methylation of alkenes a less useful method for the synthesis of amines.

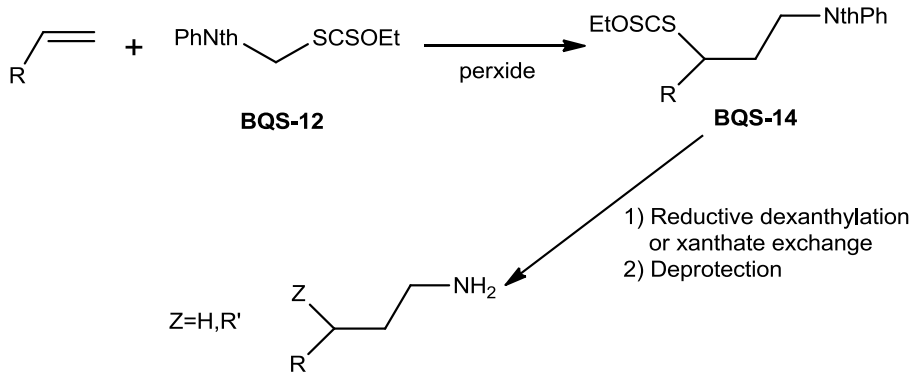


Scheme 2.33 Side reactions in hydroaminomethylation process

In contrast to the hydroaminomethylation based on metal catalyst and related methods, the approach based on xanthate chemistry outlined in Scheme 2.34 leads to the desired primary amines in a very straightforward manner and overcomes the problems mentioned above. The addition of xanthate **BQS-12** to various even unactivated olefins gives adducts **BQS-14**, and the xanthate group can be removed easily or made to undergo another radical reaction to produce more complex protected primary amines. Furthermore, the deprotection of the phthalimido by hydrazine or other suitable reagents makes the whole process strictly equal to a hydroaminomethylation of an alkene (Scheme 2.34). Therefore, the successful addition of xanthate **BQS-12** to various olefins opens up numerous possibilities to

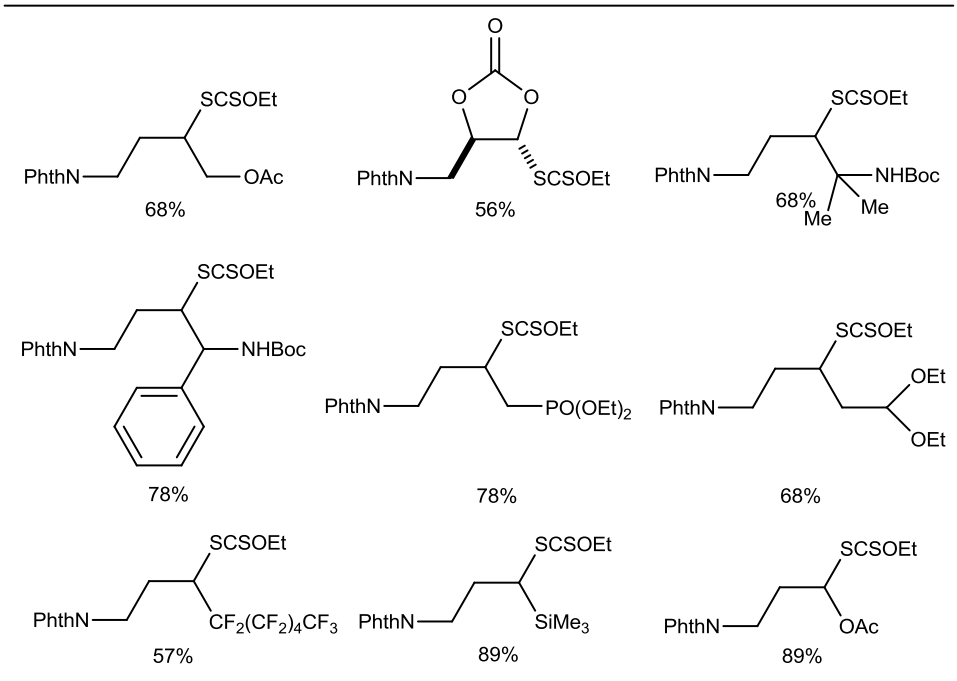
[76] (a) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem. Int. Ed.* **1990**, *29*, 558. (b) Chan, Y. N. C.; Meyer, D.; Osborn, J. A. *J. Chem. Soc. Chem. Commun.* **1990**, 869.

access highly functionalized primary amines which would be tedious to synthesize by traditional methods.



Scheme 2.34

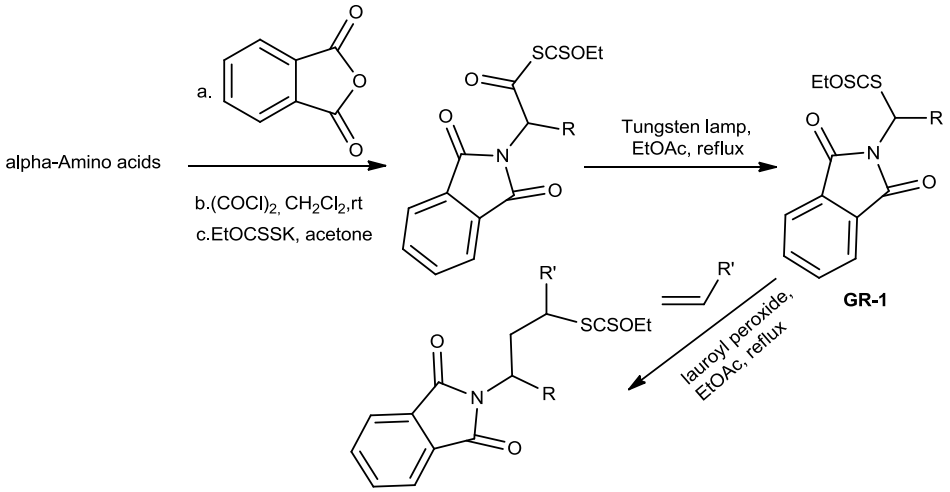
The scope of this method is illustrated by the examples in Scheme 2.35. A wide range of different functional groups such as an ester, an acetyl, a protected amino, a phosphonate, a trimethylsilyl, or a fluoroalkyl can indeed be incorporated into the adducts via this radical hydroaminomethylation of alkenes.



Scheme 2.35 Examples of phthalimidomethyl adducts

2. Xanthates from α-aminoacids

Although *S*-phthalimidomethyl xanthate, a nice crystalline solid, can be prepared from cheap and commercially available *N*-chloromethylphthalimide in one single step in high yield, the lack of generality of this method to introduce the xanthyl group at the α-position of more substituted amines encouraged us to develop other routes to this family of xanthates. Thus, Revol described the synthesis of *S*-acyl xanthates **GR-1** in three steps from the corresponding α-amino acids based on radical decarbonylation. Radical addition of xanthate **GR-1** to a broad range of alkenes proceeds efficiently to give a variety of highly functionalized, protected amines (Scheme 2.36).[77]



Scheme 2.36 Xanthates derived from α-aminoacids

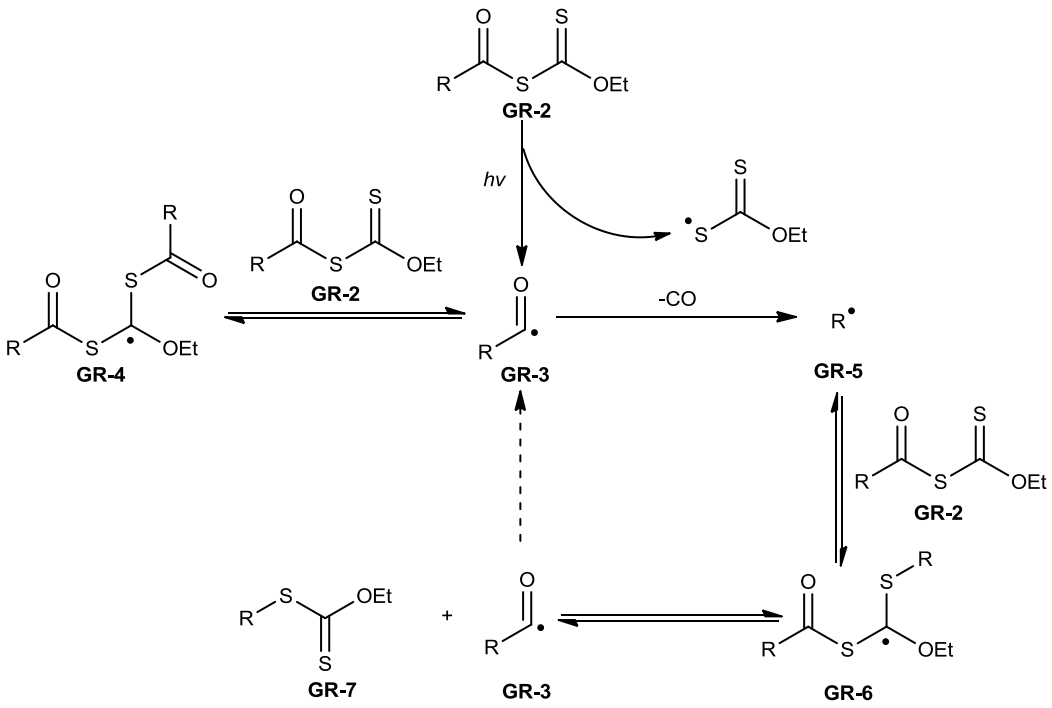
The radical decarbonylation as the key step was employed for the preparation of the xanthates and its mechanism is shown in Scheme 2.37.[78] The starting material **GR-2** undergoes homolytic cleavage upon irradiation with a tungsten lamp to give acyl radical **GR-3** which then expels carbon monoxide to generate **GR-5**.[79] The

[77] Quiclet-Sire, B.; Revol G.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 3554.

[78] Darji, R. R.; Shah, A. *Indian Journal of Chemistry* **1981**, *24*, 1077.

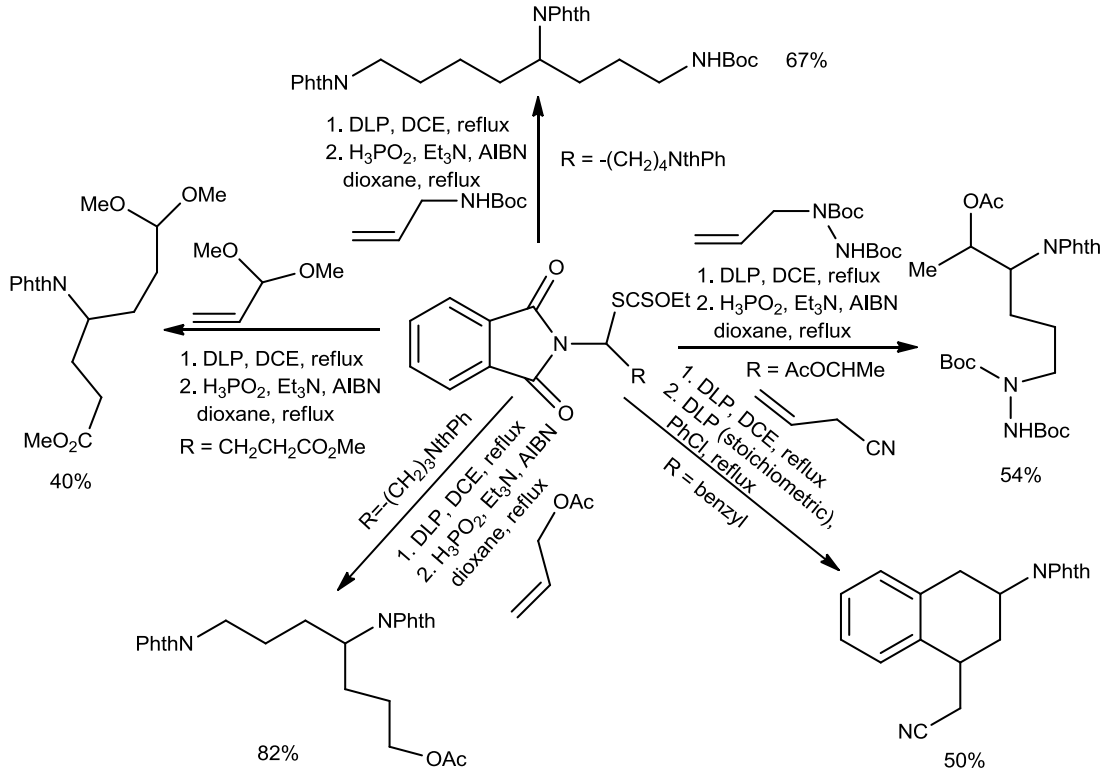
[79] (a) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967. (b) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308. (c) Heinrich, M.; Zard, S. Z. *Org. Lett.* **2004**, 6, 4969.

radical addition of **GR-5** to **GR-2** giving adduct **GR-6** is a reversible and degenerate process. Finally, the collapse of **GR-6** gives xanthate product **GR-7** and another acyl radical **GR-3** to sustain the free radical chain process.



Scheme 2.37 Decarbonylation pathway of xanthate

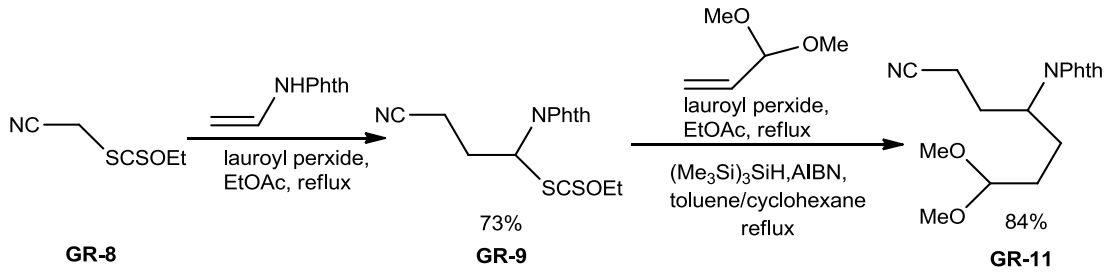
The numerous commercially available natural and unnatural α-amino acids that can be used as starting materials allow entry into a broad variety of phthalimido-substituted xanthates and following addition to alkenes, provide access to many complex amines. The scope is illustrated in Scheme 2.38 by the convergent syntheses of protected 1,4 and 1,5-diamines, γ-amino acids, β-aminoalcohols, 2-aminotetralines or triamines. It is worth noting that the stability of these *N*-phthalimido xanthates and their easy preparation on a multigram scale are further advantages of this approach.



Scheme 2.38 Synthesis of 1,4 and 1,5-diamines, *γ*-amino acids, *β*-aminoalcohols, 2-aminotetralines or triamines

3. Xanthates from the radical addition of various xanthates to *N*-vinylphthalimide

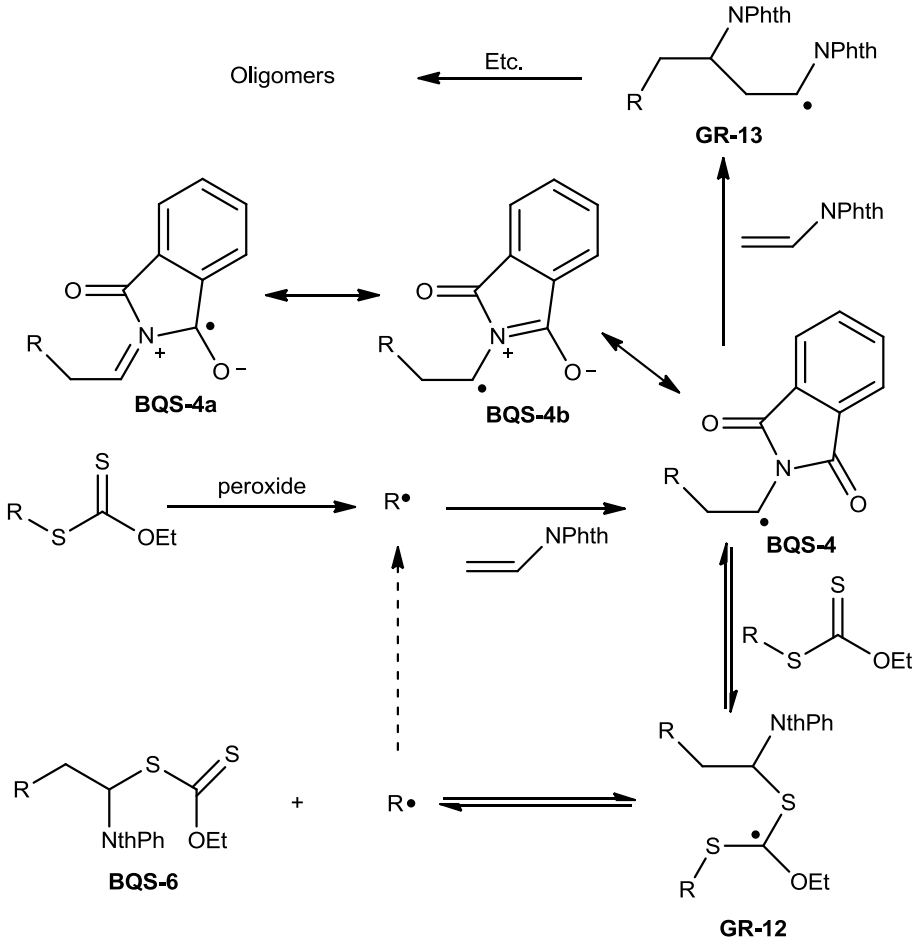
Although the addition of *N*-vinylphthalimide with many xanthates provided mostly oligomers, the successful addition of AIBN derived xanthate **GR-8** under the usual conditions encouraged us to reinvestigate the addition of other xanthates to *N*-vinylphthalimide (Scheme 2.39).[80]



Scheme 2.39 Addition of xanthate GR-8 to *N*-vinylphthalimide

[80] Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010**, *66*, 6656.

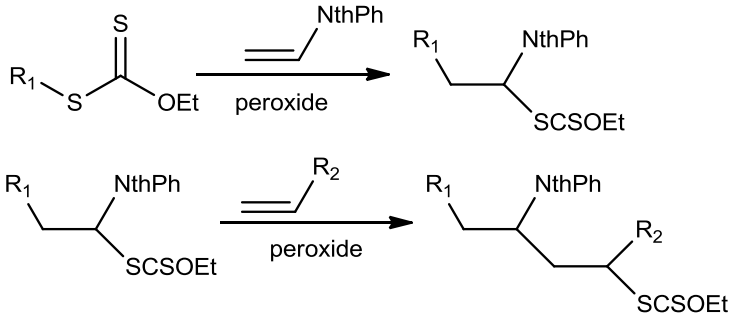
As shown in Scheme 2.40, the resonance structures of **BQS-4a** and **BQS-4b** as significant contributors increases the allylic character of radical intermediate **BQS-4** and therefore an increase of its stability is observed. Due to the fact that radical **BQS-4** is more stable than the R radical from the starting xanthate, radical **BQS-4** will undergo another radical addition with *N*-vinylphthalimido to generate radical **GR-13**, and finally furnish mostly oligomers.



Scheme 2.40 Mechanism of addition of xanthate to *N*-vinylphthalimide

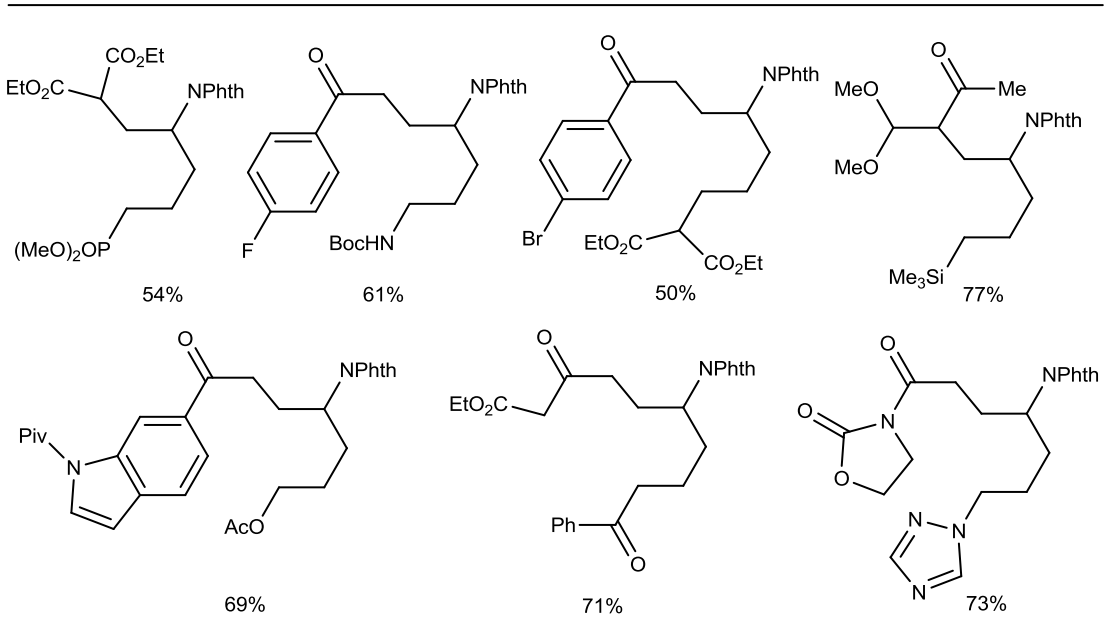
Considering that the difference between the stability of R radical and **BQS-4** must be quite small and since the olefin is often used in 1.5 to 3-fold and in some cases up to 5-fold excess, we reexamined this process by reversing the molar ratio of the xanthates to *N*-vinylphthalimide. This increases the chance of capture of radical BQS-4 to give GR-12 and therefore less oligomerization. Furthermore, by diminishing the concentration of *N*-vinylphthalimide, the possibility of a second

addition becomes even less likely. The results indeed proved that successful and efficient additions could be achieved in most cases. As summarized in Scheme 2.41, rapid combination of *N*-vinylphthalimide with different xanthates can provide various *N*-phthalimidoxanthates bearing new functional groups from the xanthate partner which can undergo further radical additions to produce even more complex protected primary amines.



Scheme 2.41 General synthetic route

As illustrated in Scheme 2.42, based on this procedure, highly functionalized amines which contain at least two different functional groups from the different reaction partners are obtained in generally good yield.

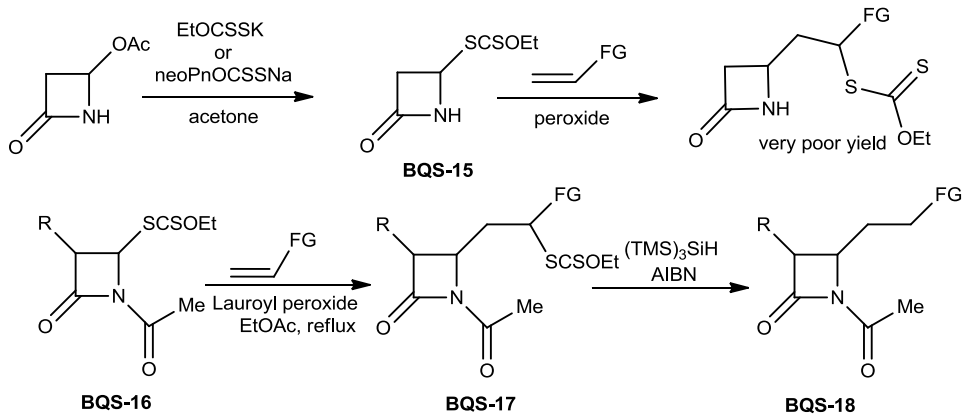


Scheme 2.42 Examples of *N*-phthalimide protected amines

4. Xanthates from other amine sources

4.1. Xanthates from *β*-lactams

β-Lactam often can be found as the core of some biologically and pharmaceutically active compounds such as penicillins, cephalosporins, carbapenems, and monobactams.[81] As a consequence, much ongoing effort has been devoted to the development of their synthesis.[82] Several years ago, a *β*-lactam derived xanthate **BQS-15** was prepared in our lab, but the addition of this xanthate furnished mostly oligomers (Scheme 2.43). The successful radical addition of *N*-phthalimidoxanthates to various unactivated olefins inspired us to introduce another carbonyl group by acylation to obtain the corresponding imide **BQS-16**. Indeed, the clean radical addition of **BQS-16** to olefins was observed, which opened up numerous opportunities to modify the initial of *β*-lactam.[83]



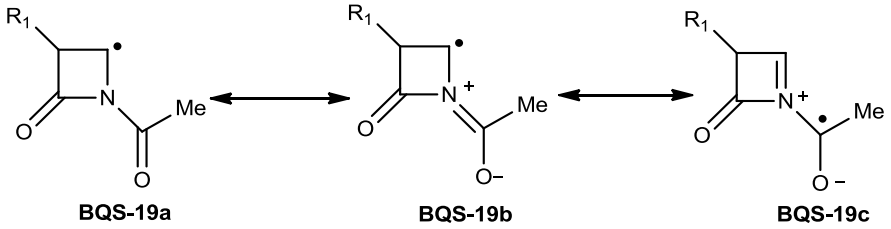
Scheme 2.43 Addition of xanthate derived from *β*-lactam to olefins

[81] (a) *Chemistry and Biology of β-Lactam Antibiotics;* Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1-3. (b) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873. (c) Buynak, J. D. *Curr. Med. Chem.* **2004**, *11*, 1951. (d) Niccolai, D.; Tarsi, L.; Thomas, R. *J. Chem. Commun.* **1997**, 2333.

[82] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (b) Dhawan, R.; Dghaym, R. D.; Syr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927. (c) Zhao, L.; Li, C.-J. *Chem. Asian J.* **2006**, *1*, 203. (d) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576. (e) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082. (f) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572.

[83] Quiclet-Sire, B.; Zard, S. Z. *Heterocycles* **2010**, *82*, 263.

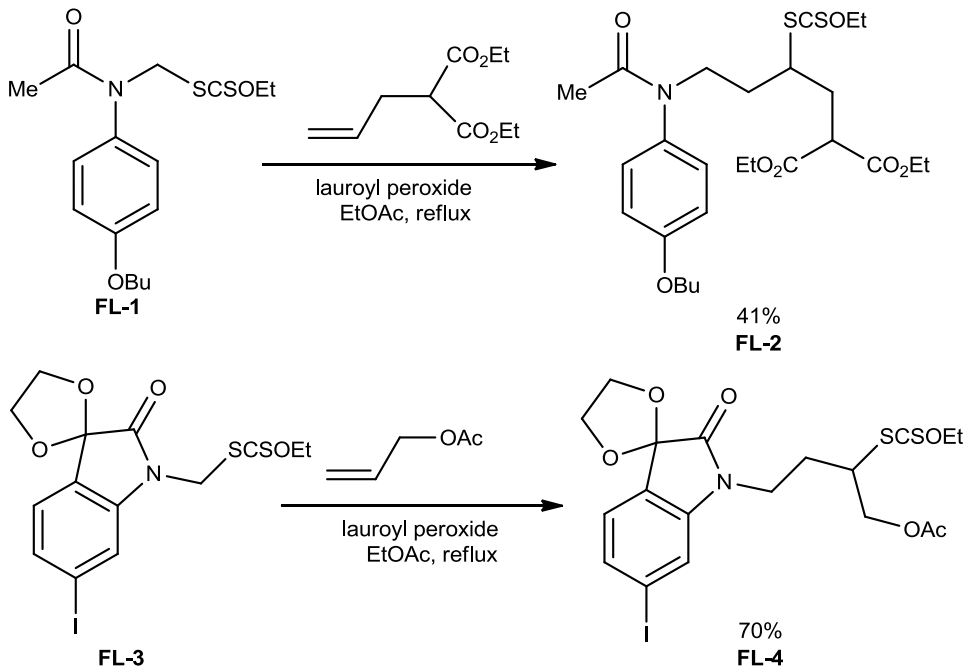
Through the resonance structures of radical intermediate **BQS-19**, we can find it possesses the same increasing allylic character similar to the carbon radical geminal to phthalimido group (Scheme 2.44).



Scheme 2.44 Resonance structures of radical intermediate **BQS-19**

4.2. Xanthate from methylanilines

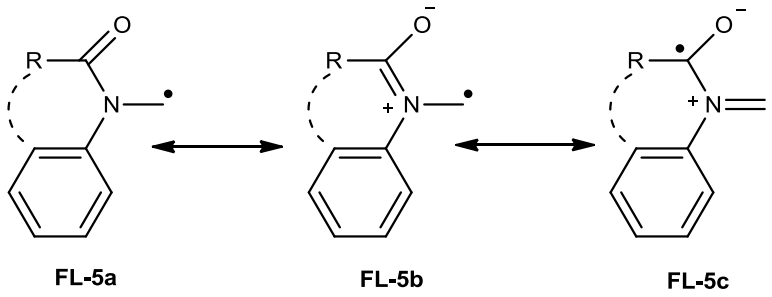
It is possible to obtain a comparable stabilisation by replacing one of the carbonyl group in the imide by an aromatic heteroamomatic ring. For example, xanthates **FL-1** and **FL-3** add clearly to various unactivated alkenes give adducts **FL-2** and **FL-4** in good yield (Scheme 2.45).



Scheme 2.45 Radical addition of xanthates FL-1 and FL-3 to olefins

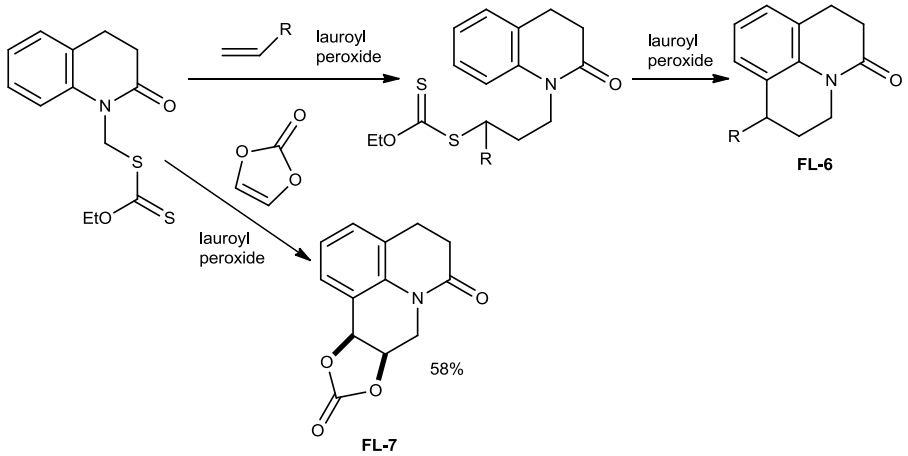
The aromatic ring provides a "vinylogous" type stabilization for radical

intermediate **FL-5** which is sufficient to allow control of the radical addition process (Scheme 2.46).



Scheme 2.46 "Vinylogous" type stabilization of **FL-5**

Interestingly, the adducts can undergo ring closure to form various polycyclic aniline derivatives. This is illustrated by the concise synthesis of compounds **FL-6** and **FL-7** depicted in Scheme 2.47.



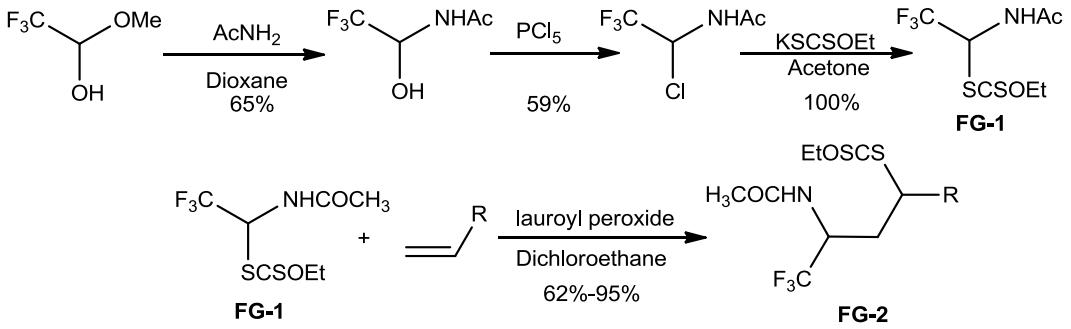
Scheme 2.47

4.3. Xanthate from α-trifluoromethylamine

As part of the continuing work for the applications of xanthate for the construction of organofluorine compounds,[84] a direct, highly flexible, and efficient

[84] (a) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573. (b) Boivin, J.; Elkaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2585. (c) Denieul, M. P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 9057. (e) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069.

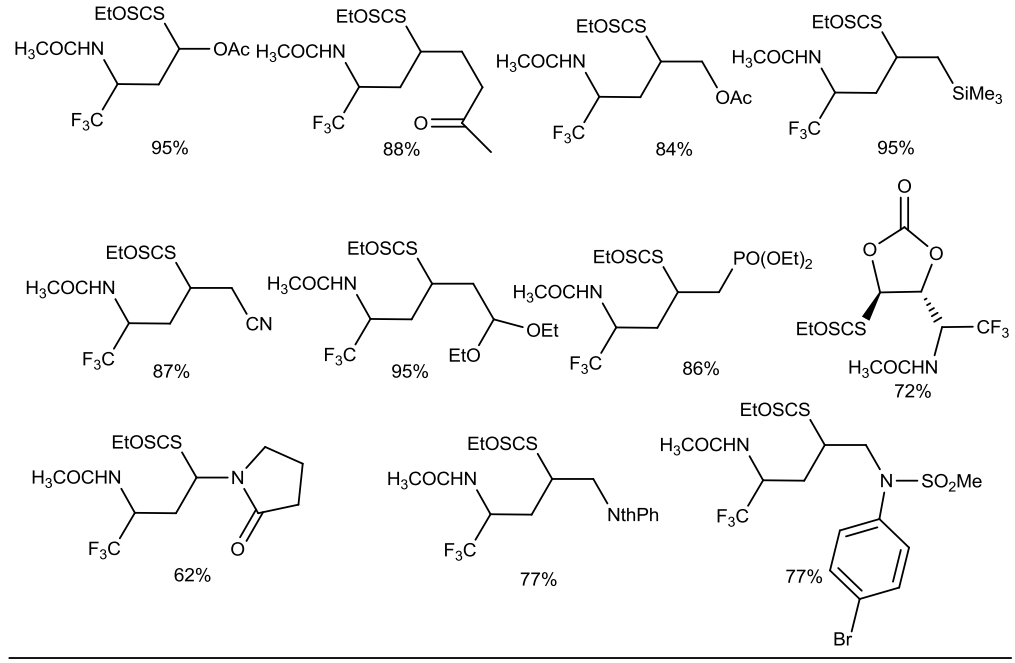
method to access α-trifluoromethylamines was developed in 2003.[85] As shown in Scheme 2.48, the trifluoromethylamine xanthate **FG-1** can be prepared in three simple steps. In this case, a second carbonyl group is not necessary since the carton-sulfur bond is sufficiently weakened by the more readily available lone pair on the nitrogen (anomeric effect). Furthermore, the electron-withdrawing trifluoromethyl group gives the radical increased electrophilic character and improves the rate of addition to the alkene partner.



Scheme 2.48 Synthesis of xanthate **FG-1** and its radical addition to olefins

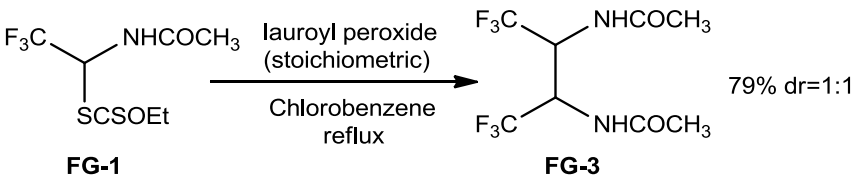
The examples outlined in Scheme 2.49 illustrate the radical addition of trifluoromethylamine xanthate **FG-1** to various olefins. A rapid and efficient introduction of trifluoromethylamine to form various complex fluorinated derivatives **FG-2** in generally high yield is now in hand.

[85] Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655.



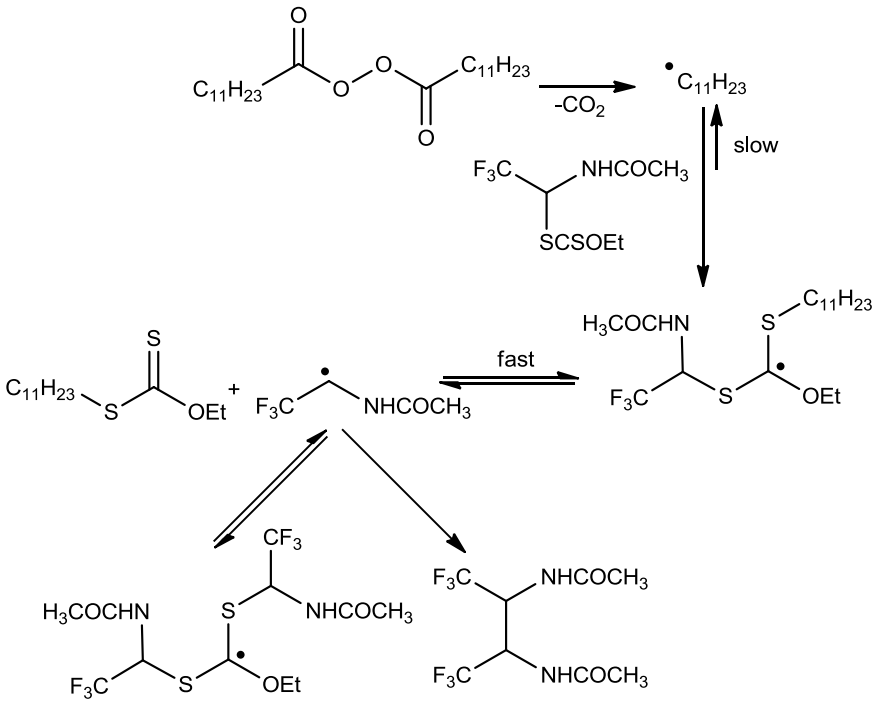
Scheme 2.49 Examples of adducts **FG-2**

Another interesting case in this study is the formation of dimer FG-3 from xanthate **FG-1**. The deprotection of **FG-3** should give a free diamine which would be a useful building block for novel ligands for transition metals (Scheme 2.50).



Scheme 2.50 Synthesis of dimer **FG-3**

A plausible mechanism for the formation of this dimer is outlined in Scheme 2.51. Since the trifluoromethylamine radical is more stable than the simple alkyl radical generated from dilauroyl peroxide, the reaction proceeds smoothly to furnish the desired dimer product.

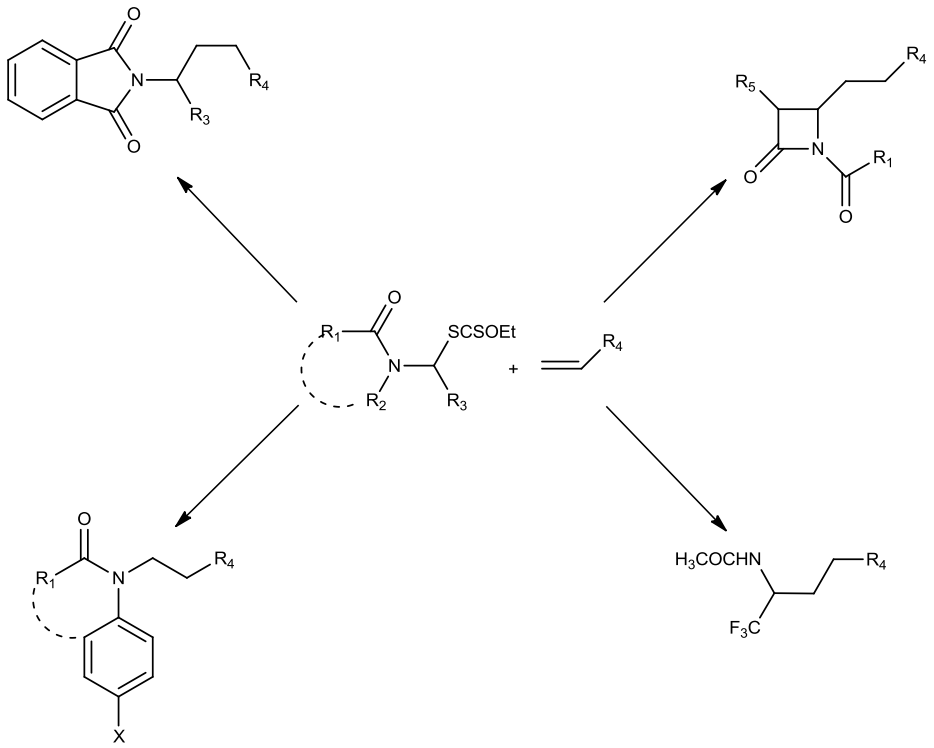


Scheme 2.51 Mechanism for the formation of dimer **FG-3**

Conclusion

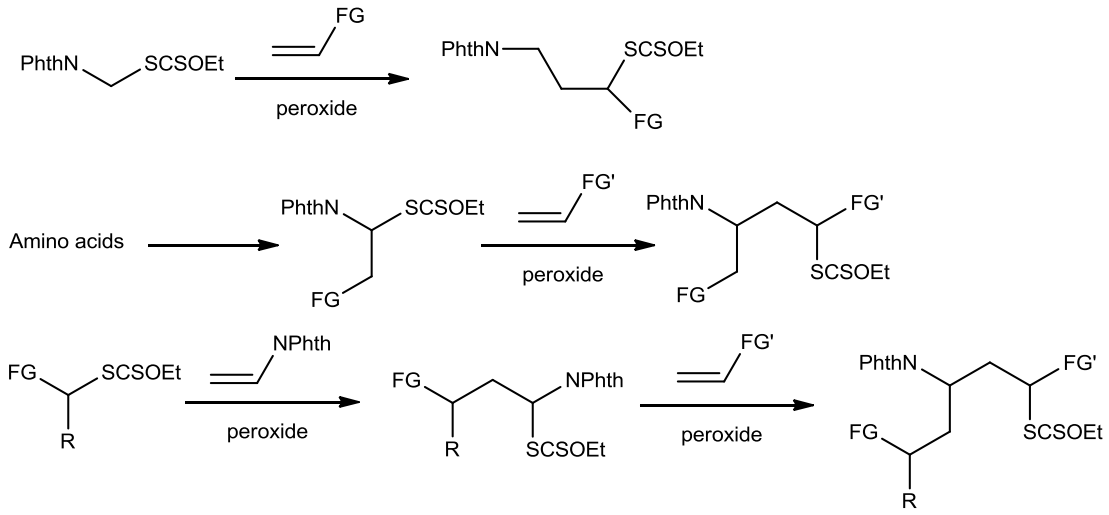
The synthesis of amines via classic named reactions and the non-radical and radical hydroaminomethylation of alkenes were briefly discussed. The radical hydroaminoalkylation of alkenes developed in our group resolves most of the problems met in most current hydroaminoalkylation methods.

The increased stability of carbon radicals geminal to an imide nitrogen atom is essential in designing radical hydroaminoalkylation processes. As illustrated in Scheme 2.52, these manners for stabilization of carbon radicals rely mainly on the introduction of a carbonyl, an aryl or a trifluoromethyl group. Many new opportunities arise for the construction of highly functionalized amines and aromatic amines.



Scheme 2.52

The three methods that have been developed are summarized in Scheme 2.53. The following chapter will detail the expansion of this approach to other substrates.


PhthN
SCSOEt
FG
peroxide
PhthN
SCSOEt
FG
Amino acids
PhthN
SCSOEt
FG
FG'
peroxide
PhthN
FG'
SCSOEt
FG
FG
SCSOEt
R
NPhth
peroxide
FG
NPhth
R
SCSOEt
FG'
peroxide
PhthN
FG'
FG
SCSOEt
R

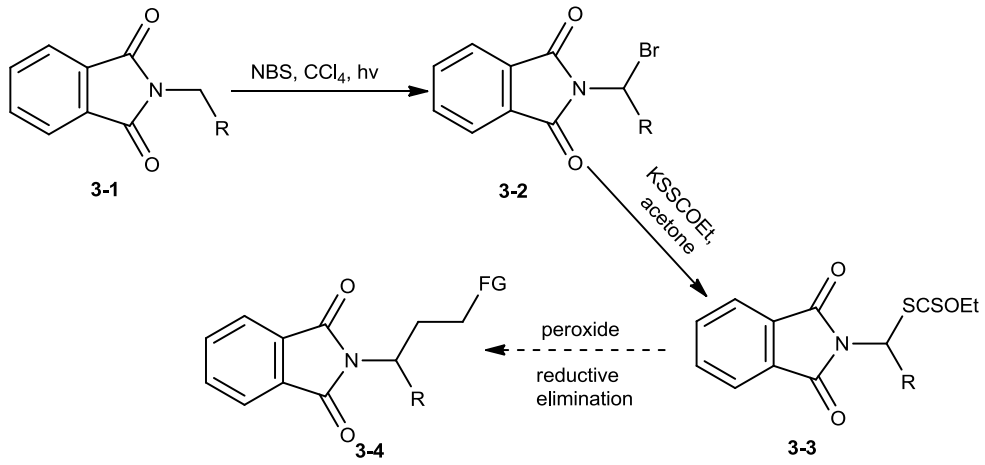
Scheme 2.53

Chapter 3

Amines synthesis via the Combination of the Wohl-Ziegler Reaction with Xanthate Chemistry

Introduction

Carbon radicals stabilized by a phthalimido group possesses a small but nevertheless significant allylic character, which allow the efficient intermolecular radical addition of phthalimido-substituted xanthates to various unactivated alkenes. Although we have applied this feature to the synthesis of numerous phthalimide protected amines, it was important to expand the pool of obtaining xanthates to members not readily available by the previous methods. We were therefore intrigued by the bromination of **3-1** to form bromide **3-2** via the classical Wohl-Ziegler allylic bromination process. Displacement of bromine by xanthate group would afford the corresponding xanthate **3-3,** which could then be employed in the typical radical additions to alkenes. This potentially flexible and general route for the construction of complex amines is generalized in Scheme 3.1.



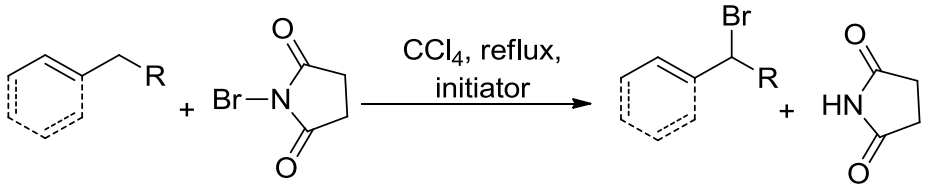
Scheme **3.1** The synthesis of xanthates via Wohl-Ziegler bromination

In view of the large pool of commercially available or easily accessible primary amines, success of the Wohl-Ziegler reaction in one case would considerably expand this approach to complex amines.

Ⅰ. Bromination of *N*-phthalimide protected amines via the Wohl-Ziegler reaction

1. The Wohl-Ziegler reaction

In 1942, Ziegler developed a bromination process by using *N*-bromosuccinimide as a convenient brominating agent. Several years later Karrer found that the addition of a small amount of dibenzoyl peroxide significantly increased the reaction rate and the scope of this reaction was greatly extended.[85] Quickly chemists recognized that this reaction proceeded by a free radical chain process. Nowadays, the Wohl–Ziegler reaction has been defined as a reaction between an allylic or benzylic substrate with *N*-bromosuccinimide (NBS) under radical initiating conditions which can provide the corresponding allylic or benzylic bromide (Scheme 3.2).[86]



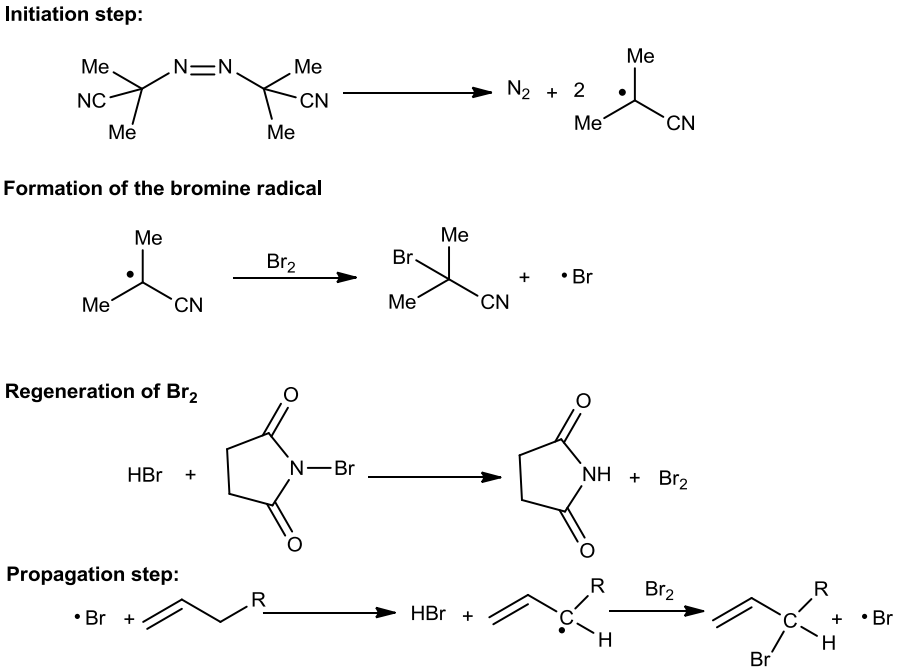
Scheme 3.2 Wohl-Ziegler reaction

As shown in the scheme 3.3, heating a solution of AIBN releases nitrogen gas and leads to the formation of two *tert*-butyronitrile radicals. These radicals readily react with the small amount of Br_2 present in the NBS to form a bromine atom. Light or heat may be used to initiate the reaction instead of AIBN or other initiators. In the following propagation step, the bromine atom abstracts an allylic hydrogen forming a stable allylic radical and HBr. This latter reacts immediately with NBS to maintain the low concentration of Br_2 which plays an essential role in sustaining the chain process.

[85] (a) Wohl, A. *Ber*. **1919**, *52*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber.* **1921**, *54*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Ann*. **1942**, *551*, 80. (d) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573.

[86] (a) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271. (b) Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863.

Since a high concentration of Br_2 would lead to the bromination of the double bond, a low concentration of Br_2 is therefore critical for an efficient bromination.

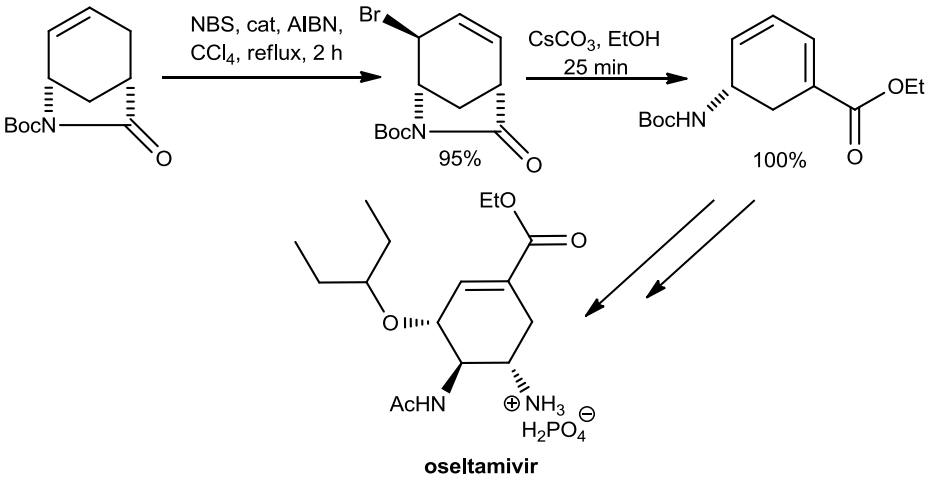


Scheme 3.3 Mechanism of Wohl-Ziegler reaction

2. The Wohl-Ziegler reaction in organic synthesis

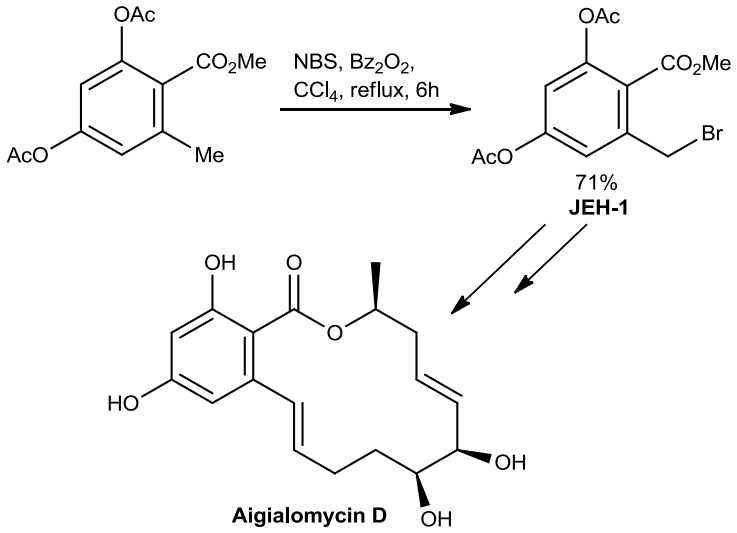
Numerous brominations have been reported over the past decades, using the Wohl-Ziegler. The following studies demonstrate the wide applicability of this reaction. In the synthesis of oseltamivir, an anti-influenza neuramidase inhibitor, Corey and co-workers constructed the 1,3-cyclohexadiene intermediate via a Wohl-Ziegler bromination and elimination (Scheme 3.4).[87] A 95% yield of the brominated product attests to the efficiency that can be attained by this reaction.

[87] Yeung, Y. Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* *2***006**, 12*8*, 6310.



Scheme 3.4 Total synthesis of the oseltamivir involving a Wohl-Ziegler bromination

Harvey and co-workers applied the Wohl-Ziegler bromination in the course of the total synthesis of aigialomycin D (Scheme 3.5).[88] The benzylic bromide **JEH-1** as a key intermediate was synthesized via a Wohl-Ziegler reaction. Instead of AIBN, benzoyl peroxide was used as an initiator in this reaction.

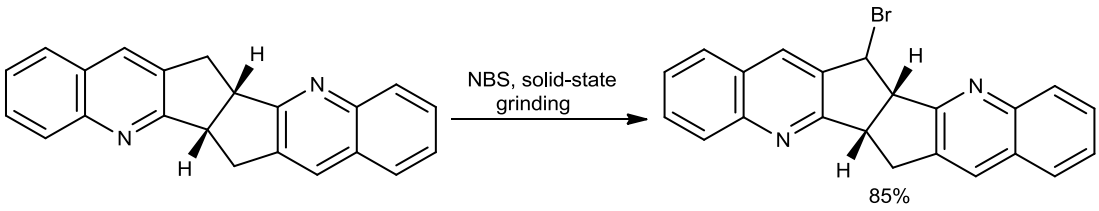


Scheme 3.5 Total synthesis of aigialomycin D involving a Wohl-Ziegler bromination

Despite many applications of Wohl-Ziegler reaction in organic synthesis, some unsolved problems have somewhat limited the further applications of this reaction. Carbon tetrachloride is the most commonly used solvent in the Wohl-Ziegler reaction, but the toxic and ozone-depleting properties of carbon tetrachloride have made it less

[88] Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271.

available and encouraged chemists to find alternative solvents. One solvent free Wohl-Ziegler reaction was developed by Rahman and co-workers as shown in Scheme 3.6. Using this solid-solid Wohl-Ziegler reaction, the bromination of diquinoline was completed in high yield.[89]



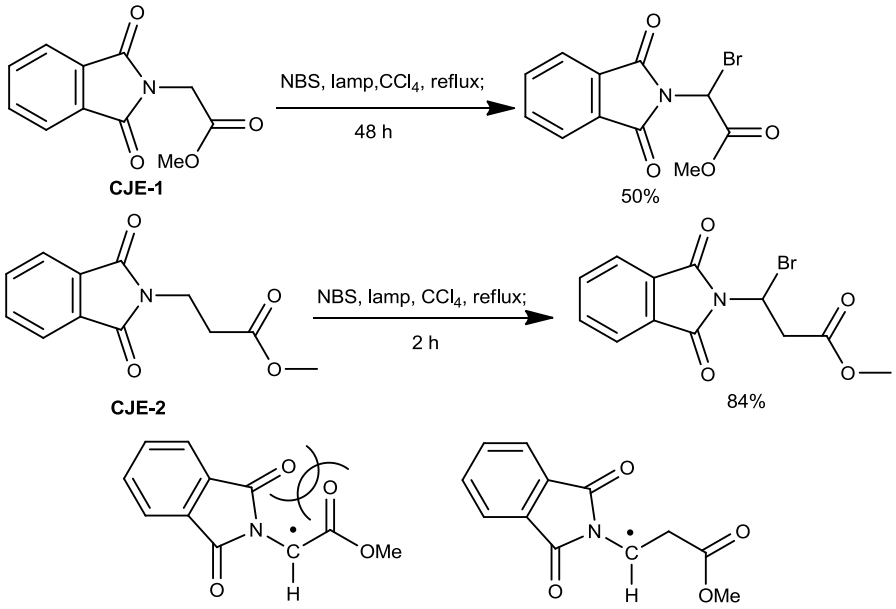
Scheme 3.6 Wohl-Ziegler reaction in the absence of solvent

3. Bromination of *N*-phthalimide protected amines based on the Wohl-Ziegler reaction

The application of the phthalimido as a protecting group to assist the synthesis of amines is extensively documented in the literature. In 1898, Sachs prepared *N*-bromomethylphthalimide from *N*-methylphthalimide by using bromine as the brominating agent; however, under the same conditions, *N*-ethylphthalimide gave only *N*-tribromoethylphthalimide. [90] In 1954, Zaugg successfully obtained *N*-(2-bromoethyl)-phthalimide in high yield from *N*-ethylphthalimide via Wohl-Ziegler synthetic method, which was the first bromination of *N*-alkylphthalimide via Wohl-Ziegler synthesis.[91] In 1989, Easton and co-workers examined the bromination of a wide range of amino acid derivatives including *N*-phthalimide protected amino acid by using *N*-bromosuccinimide as the brominating agent.[92] By comparing the rates of bromination, they discovered how different substituents influenced the stability of the radical intermediates generated from the protected amine substrates.[93] Therefore, this study inspired us to synthesize novel phthalimide protected amine xanthates via the Wohl-Ziegler reaction. Furthermore,

[89] Rahman, A. N. M. M.; Bishop, R.; Tan, R.; Shan, N. *Green Chem.*, **2005**, *7*, 207.
[90] Sachs, F. *Ber*. **1898**, *31*, 1225.
[91] Zaugg, H. E. *J. Am. Chem. Soc.*, **1954**, *76*, 5818.
[92] Burgess, V. A., Easton, C. J., Hay, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 1047.
[93] Easton, C. J., Hutton, C.A., Rositano, G., Tan, E. W. *J. Org. Chem.* **1991**, *56*, 5614.

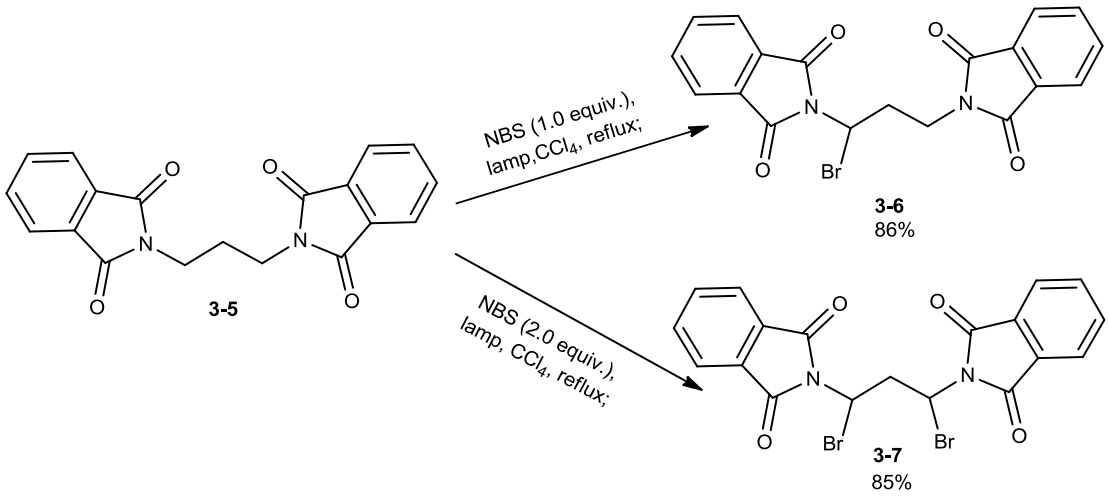
they described the bromination of phthalimide protected *α*-amino acid **CJE-1** was quite inefficient, and required 48 h to achieve 50% conversion; however, the bromination of *β*-amino acid **CJE-2** was completed with high efficiency in 84% yield (Scheme 3.7). A plausible explanation was then proposed. As described in Scheme 3.7, the steric effect arising from the interaction of the methoxycarbonyl and phthalimidyl group would destroy its planar configuration resulting in less efficient delocalization of the unpaired electron.



Scheme 3.7 Bromination of **CJE-1** and **CJE-2**

According to the literature procedure we prepared bromination product **CJE-2** and then extended this study to find other suitable amine substrates for the preparation of the corresponding xanthates via the same bromination approach. The decarboxylation process previously described was used to obtain the 1,4-diaminobutyl and 1,5-diaminopentyl xanthates but other synthetically interesting xanthates derived from 1,2-diaminoethane and 1,3-diaminopropane are not readily accessible by this route because the precursor aminoacids are not available. Thus, we tested the bromination of di-phthalimide protected 1,3-diaminopropane **3-5** which afforded the mono-bromo-product **3-6** in high yield. If a little more than exactly one equivalent

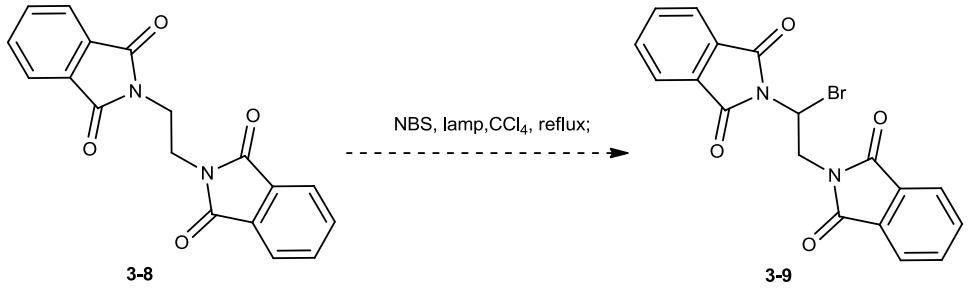
NBS with respect to the amine was added, then a small amount of the di-bromo-product **3-7** was observed (Scheme 3.8). To convert all the starting material **3-5** to di-bromo-product **3-7**, two equivalents of NBS were required.



Scheme 3.8 Bromination of **3-5**

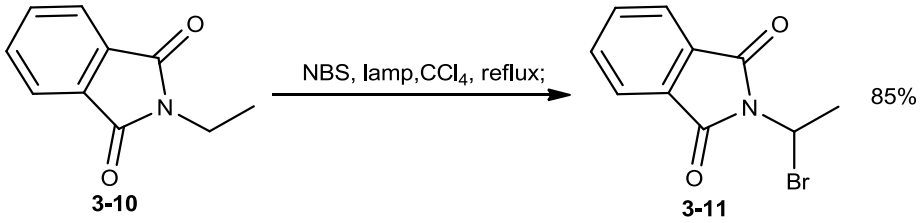
With compound **3-6** and **3-7** in hand, we tried to accomplish the synthesis of the mono-bromo 1,2-diaminoethane derivative in the same manner, but *N*-phthalimide protected 1,2-diamine **3-8** was only slightly soluble in CCl_4 which prevented the bromination process (Scheme 3.9). Even under quite dilute conditions, the starting material **3-8** still remained largely insoluble and then, in the presence of light and a small amount of AIBN, the starting material remained unaffected without any trace of bromination product observed, even after a quite long time. Since compound **3-8** was soluble in chloroform, we added dropwise chloroform to the refluxing CCl_4 mixture until all the starting material was totally dissolved. After 10 h, trace amounts of the desired bromide **3-9** were observed in the crude NMR spectrum. However, after an additional 10 h, the NMR spectrum showed that the ratio of **3-8** to **3-9** remained the same. Replacing totally the solvent with chloroform, again after 10 h starting material **3-8** remained unchanged. Probably, this unsuccessful bromination suffered from the same problem as the bromination of *N*-phthalimide protected glycine ester, but the exact reason is still unclear. It could also be due to a mismatch of polar effects, with

one phltalimide group acting as an electron-withdrawing (by induction) towards the adjacent position.



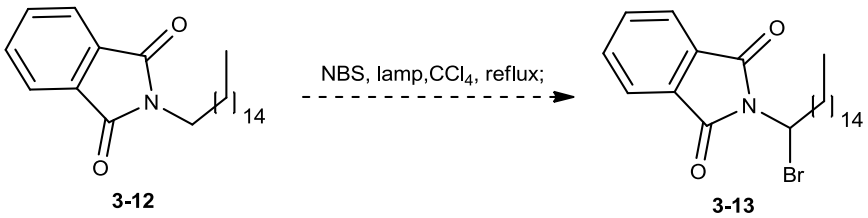
Scheme 3.9 Bromination of **3-8**

We next turned our attention to the bromination of the simple *N*-phthalimide protected alkyl amine like **3-10**, devoid of the unfavorable influence of other functional groups. The bromination was indeed completed as we expected in high yield (Scheme 3.10).



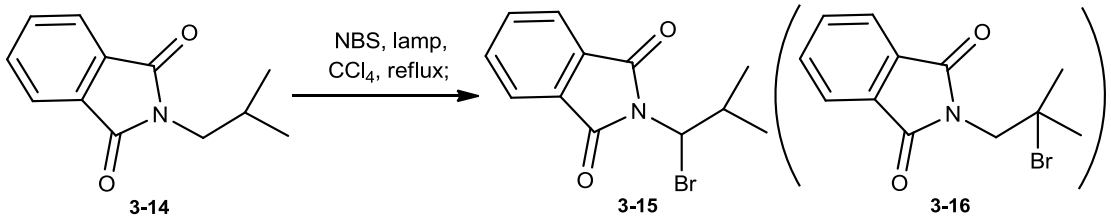
Scheme 3.10 Bromination of **3-10**

Then, we extended our study to *N*-phthalimide protected alkyl amines such as **3-12** bearing a long chain (Scheme 3.11). Although the starting material was partial consumed after 5 h, besides **3-12** a undetermined mixture was obtained. Zaugg attributed this to the non-specific substitution which meant that increasing length of the alkyl substituent made the bromination unselective. Thus, if the alkyl chain contains less than six carbons, then a high yield will be guaranteed, but longer chain will give mixtures.



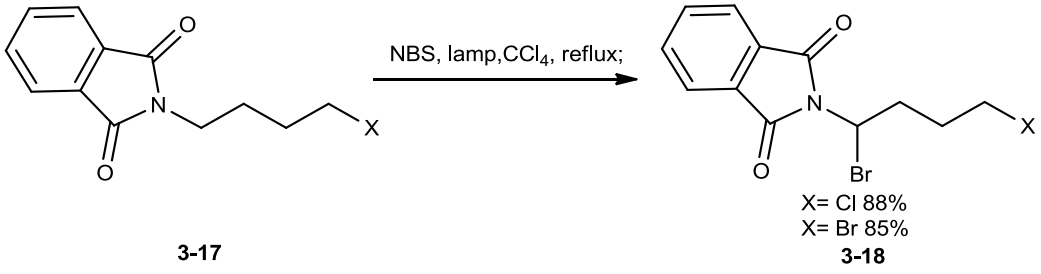
Scheme 3.11 Bromination of **3-12**

It is a great interesting to compare the stability of tertiary carbon radicals with carbon radicals geminal to phthalimido groups, and this encouraged us to test the bromination of **3-14** bearing a tertiary carbon (Scheme 3.12). Whereas **3-14** was totally consumed in 5 h, no desired product **3-15** was observed. The crude NMR spectrum indicated that probably a small part of the starting material was converted into **3-16**, which suggested that the tertiary carbon radical is more stable than the carbon radical stabilized by a phthalimido group.



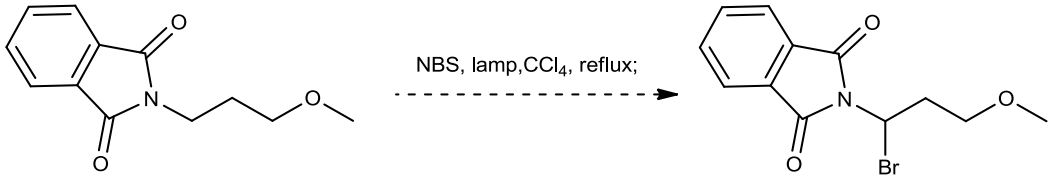
Scheme 3.12 Bromination of **3-14**

With better knowledge about bromination of *N*-alkyl substituted phthalimides, we examined phthalimides bearing other heteroatoms such as oxygens or halogens. As illustrated in Scheme 3.13, the bromination of substrates **3-17** containing a chlorine or a bromine atom proceeds smoothly to furnish the desired products **3-18** in good yield.



Scheme 3.13 Bromination of **3-17**

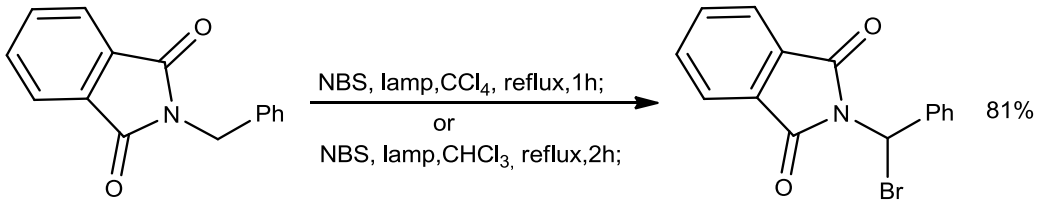
However, bromination of **3-18** did not give the desired product **3-19** (Scheme 3.14). After 7 h, the starting material **3-18** was totally consumed via the same approach, but the crude NMR spectrum showed only undetermined mixture. It is possible that the electrophilic bromine atom prefers to abstract a hydrogen from the carbon geminal to the oxygen atom leading to the formation of a nucleophilic radical.



3-18 **3-19**

Scheme 3.14 Bromination of **3-18**

We also attempted to prepare the xanthate from benzylamine in the same manner. The high stability of benzylic radical should promote the desired reaction. Indeed, the bromination of **3-20** was completed within one hour (Scheme 3.15). Furthermore, chloroform, as a more environmentally benign solvent, could be used for this bromination reaction instead of carbon tetrachloride, but a longer reaction time was required to consume all of phthalimide **3-20**.



3-20 **3-21**

Scheme 3.15 Bromination of **3-20**

The study of bromination of *N*-phthalimide protected amine derivatives to give geminal phthalimido-bromo derivatives improved our understanding of the stability of carbon radicals geminal to phthalimido groups. This knowledge is very useful in the context of the present xanthate chemistry.

Ⅱ. Radical synthesis of *β*-amino acids, alkylamines, 1,3-diamines and polyamines

1. Radical synthesis of *β*-amino acids

1.1. *β*-Amino acids

β-amino acids are highly valuable substances from a medicinal chemistry perspective, since they are often found in natural products and pharmaceuticals.[94] Several pharmaceutical products are displayed in Figure 3.1 Phenoxymethylpenicillin, commonly known as penicillin V, has a range of antimicrobial activity against Gram-positive bacteria; TAN-1057 A as a dipeptide antibiotic is specifically active against staphylococcus species including methicillin-resistant strains; Sitagliptin **(**trade name Januvia), an enzyme-inhibiting drug, is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for the treatment of diabetes mellitus type 2 with fewer side effects in the control of blood glucose levels.

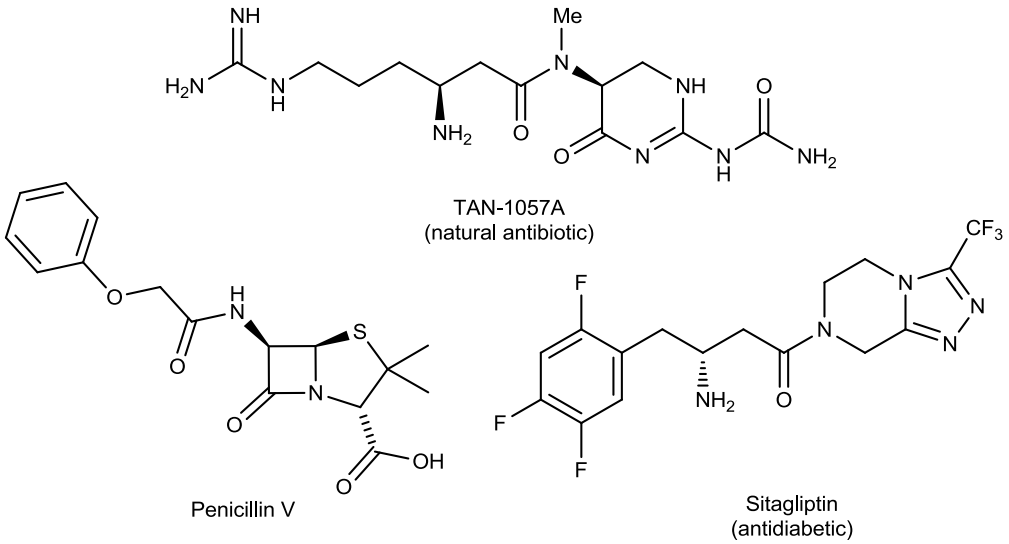
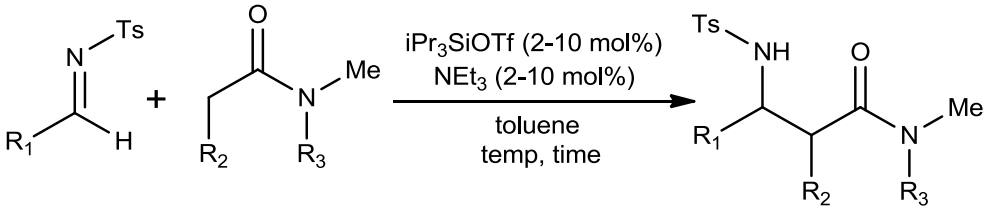


Figure 3.1 Examples of pharmaceutical products

[94] (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley: New York, 1997. (c) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; Wiley: Hoboken, NJ, 2005.

1.2. Recent approaches for the synthesis of *β*-aminoacids

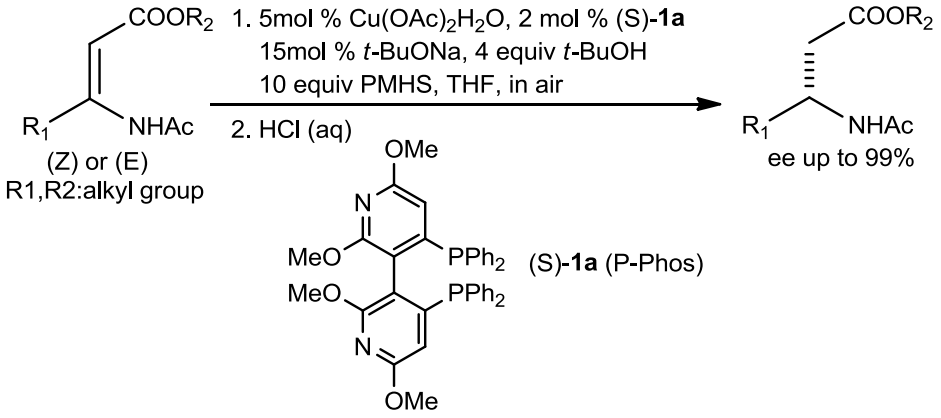
Traditionally, silicon enolates require stoichiometric amounts of the reactive silicon species, but Kobayashi and co-workers described a Mannich-type reaction to give various *β*-amino acids based on a silicon catalyzed process.[95] In the presence of a catalytic amount of trimethylsilyl triflate and triethylamine, this Mannich reaction with various imines occurs even with the less acidic *α*-position of amides to afford the corresponding *β*-amino acids (Scheme 3.16).



Scheme 3.16 The synthesis of *β*-amino acids via Mannich-type reaction

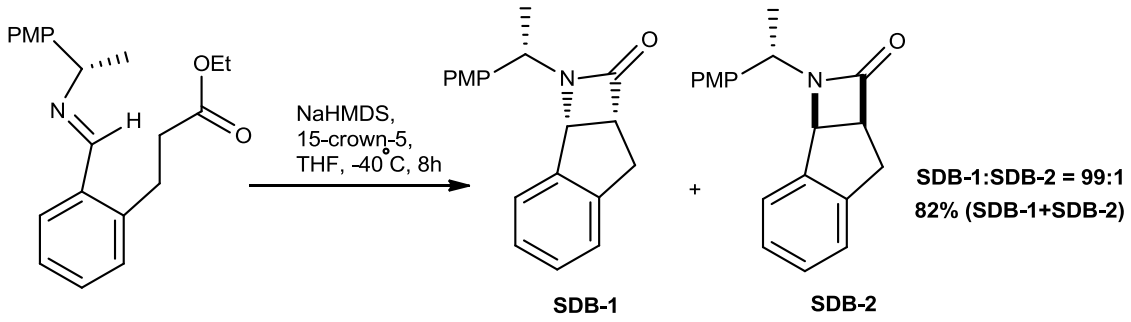
Recently, Chan and co-workers accomplished the synthesis of *β*-alkyl-*β*-amino acid derivatives via the asymmetric 1,4-reduction of *β*-(acylamino)acrylates using a copper-catalyzed process.[96] As shown in Scheme 3.17, in the presence of 5 mol% copper(II) acetate monohydrate ($Cu(OAc)_2H_2O$) together with 2 mol% *(S)*-**1a** as the catalyst, and 10 equiv of polymethylhydrosiloxane (PMHS), either (Z) or (E)-*β*-(acylamino) acrylates were reduced to the highly enantiopure *β*-alkyl-*β*-amino acids under mild conditions.

[95] Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708.
[96] Wu, Y.; Qi, S.-B.; Wu, F. F.; Zhang, X.; Li, M.; Wu, J.; Chan, A. S. C. *Org. Lett.* **2011**, *13*, 1754.



Scheme 3.17 The synthesis of *β*-amino acids via copper-catalyzed process

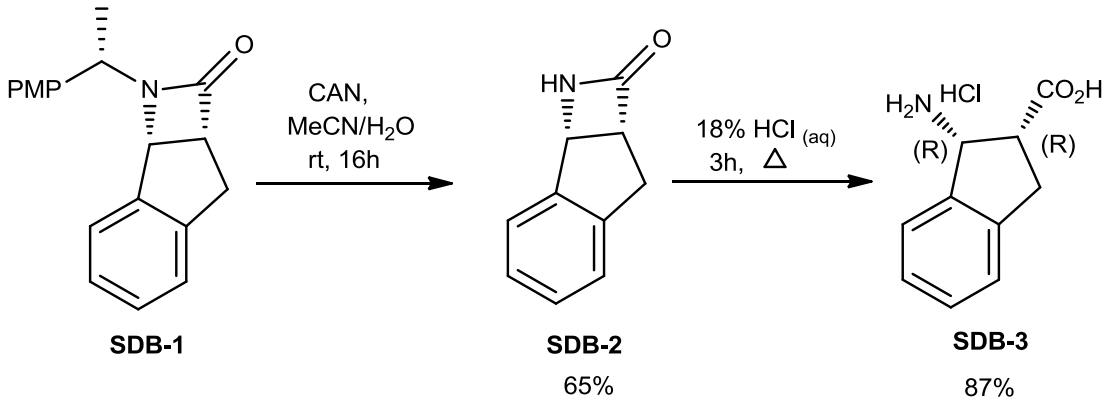
The ring opening of *β*-lactams provides another possibility for the synthesis of *β*-amino acids. Bull and co-workers described a highly diastereoselective intramolecular cyclization of imino-esters which afforded *β*-lactams **SDB-1** in the presence of base (Scheme 3.18).[97]



Scheme 3.18 Intramolecular cyclization of imino-esters

The deprotection of **SDB-1** was realized by using ceric ammonium nitrate (CAN) to afford corresponding *β*-lactam **SDB-2** which was then converted to *β*-amino acids **SDB-3** under acidic conditions in high yield.

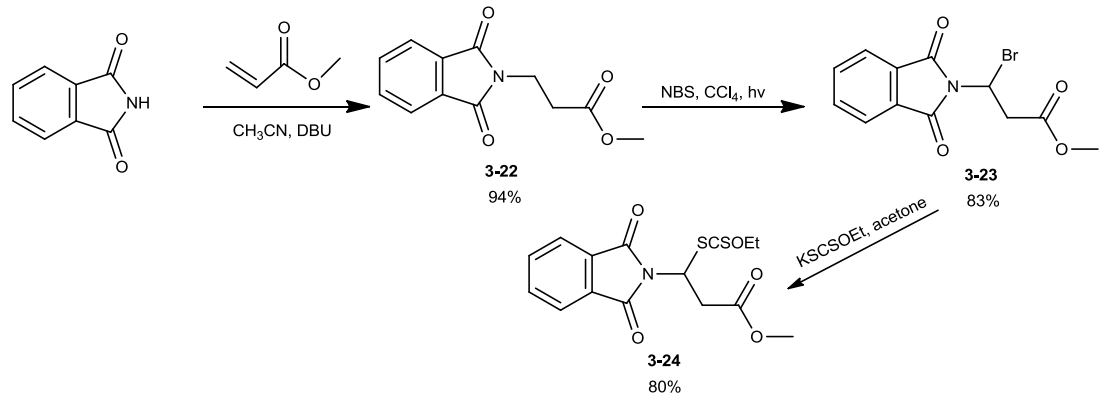
[97] Evans, C. D.; Mahon, M. F.; Andrews, P. C.; Muir, J.; Bull, S. D. *Org. Lett.* **2011**, *13*, 6276.



Scheme 3.19 Ring opening of **SDB-1**

1.3. Synthesis of *β*-amino acids based on xanthate chemistry[98]

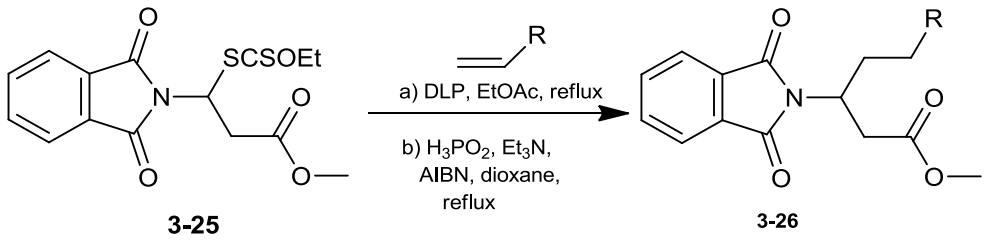
Based on previous studies on radical hydroaminomethylation of alkenes and bromination of the various phthalimido protected amines via the classical Wohl-Ziegler allylic bromination using *N*-bromosuccinimide (NBS), we extended this radical hydroaminomethylation approach to the synthesis of *β*-amino acid derivatives. As shown in the Scheme 3.20, the **3-22** was rapidly prepared via Michael addition of phthalimide with methyl acrylate in the presence of DBU.[99] Next, bromination of **3-22** gave **3-23** and then replacement of bromine by potassium ethyl xanthate furnished the desired xanthate product **3-24**.



Scheme 3.20 The synthesis of xanthate **3-24**

[98] Preliminary results were attained by Rachel A. Jones.
[99] Yeom, C.-E.; Kim, M. J.; Kim, B. M.; *Tetrahedron*, **2007**, *63*, 904.

Addition of xanthate **3-25** to various alkenes gave various adducts which underwent reductive removal of the xanthate group by triethylammonium hypophosphite to furnish the corresponding *N*-phthalimide protected *β*-amino acid derivatives (Scheme 3.21).

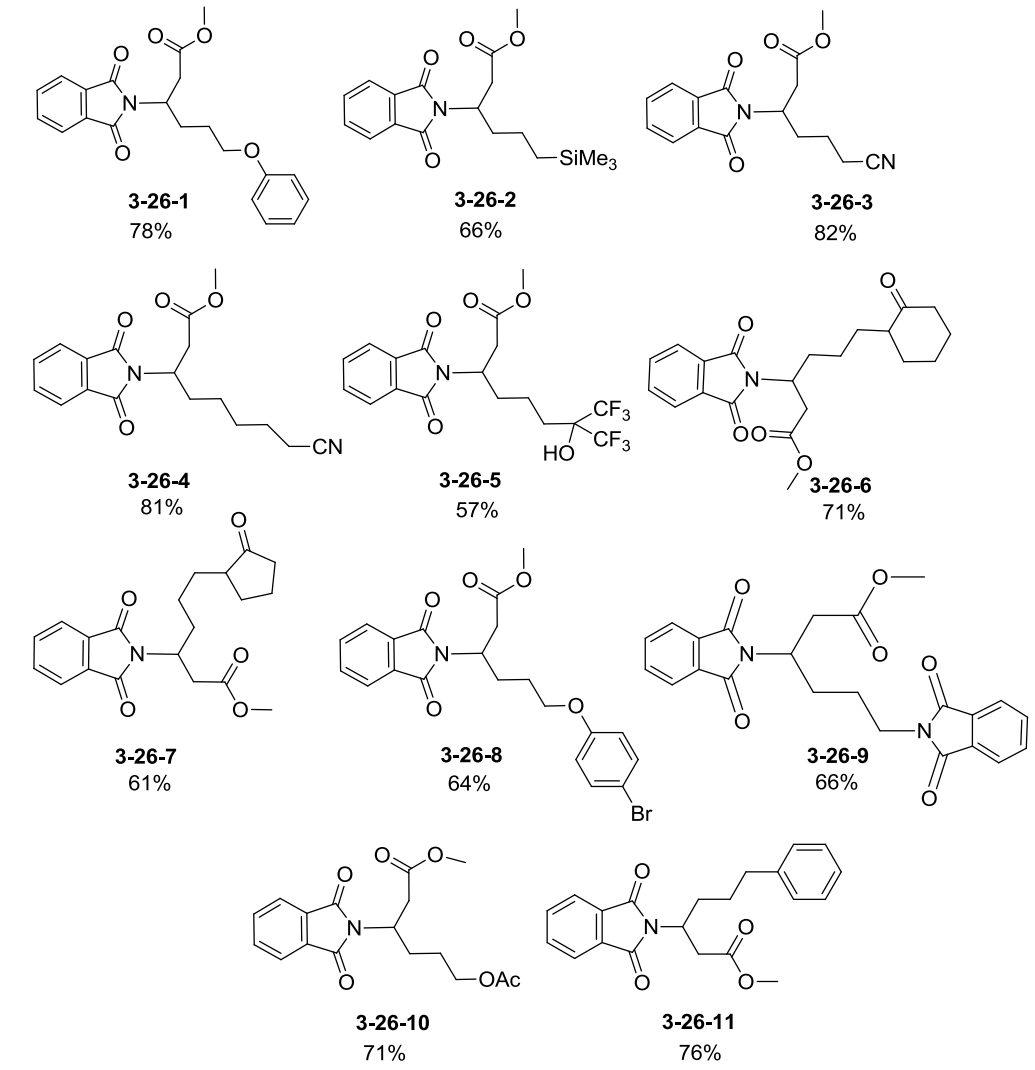


Scheme 3.21 Radical addition of **3-25** to olefins

A wide range of functional groups, such as trimethylsilyl, cyano, ketonyl, trifluoromethyl, ester or alicyclic groups like cyclohexanyl and cyclopentanyl, or aromatic rings like phenoxy or phenyl are incorporated into the *N*-phthalimide protected amino acids, as illustrated in Scheme 3.22. It is worthwhile to note that **3-26-9** corresponds to methyl *β*-lysinate with the two amino groups protected as phthalimides. *β*-Lysine (or isolysine) is present in blood platelets during coagulation and in tears, and acts as an antibiotic by causing lysis of numerous Gram-positive bacteria.[100] It has been found as key components in a range of antibiotics such as streptothrycin F, racemomycins and viomycin.[101] There has therefore been an increasing interest for its synthesis, and our approach provides a quite concise and efficient route to access phthalimido protected *β*-lysine in two steps.

[100] Spiteller, P.; von Nussbaum, F. *β*-Amino Acids in Natural Products. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E.; Soloshonok, V. Eds.; Wiley: Hoboken, NJ, 2005; pp 19-91.

[101] (a) Gould, S. J.; Thiruvengadam, T. K. *J. Am. Chem. Soc.* **1981**, *103*, 6752. (b) Thiruvengadam, T. K.; Gould, S. J.; Aberhart, D. J.; Liu, H.-J.; *J. Am. Chem. Soc.* **1983**, *105*, 5470. (c) Y. Sawada and H. Taniyama, *Chem. Pharm. Bull.* **1977**, *25*, 1302.

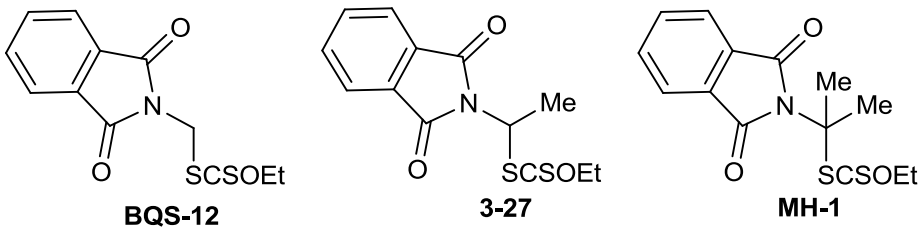


Scheme 3.22 *N*-Phthalimide protected *β*-amino acids

2. Radical synthesis of alkylamine

In chapter 2 we have already discussed the radical addition of phthalimido-substituted amine xanthate **BQS-12** to various alkenes. In another previous study we examined the addition of xanthate **MH-1**.[102] In these cases a primary and a tertiary carbon radical is generated. To better understand the difference in their behaviours, xanthate **3-27** was therefore prepared and its radical addition to unactivated olefins investigated (Scheme 3.23).

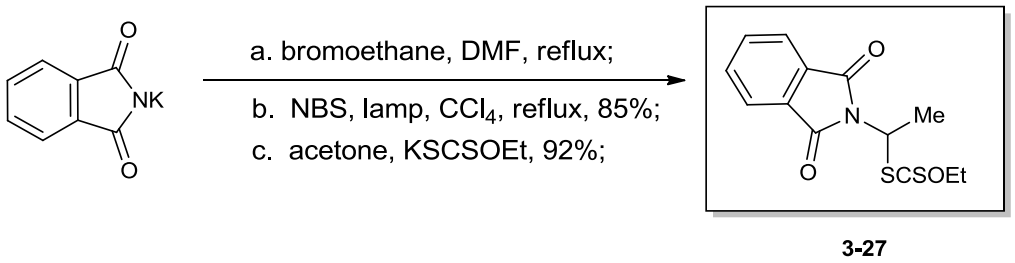
[102] Heinrich, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 4969.



BQS-12 **3-27** **MH-1**

Scheme 3.23 Primary, secondary and tertiary phthalimido-substituted xanthates

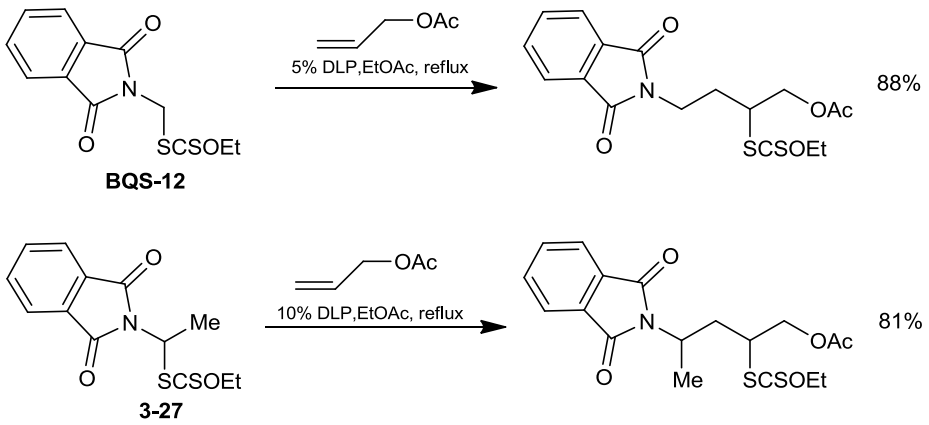
As illustrated in Scheme 3.24, the preparation of xanthate **3-27** was quite straightforward. The *N*-phthalimide protected amine was prepared by Gabriel synthesis and then it would proceed to afford xanthate **3-27** via Wohl-Ziegler bromination and replacement of bromine by xanthate group.



3-27

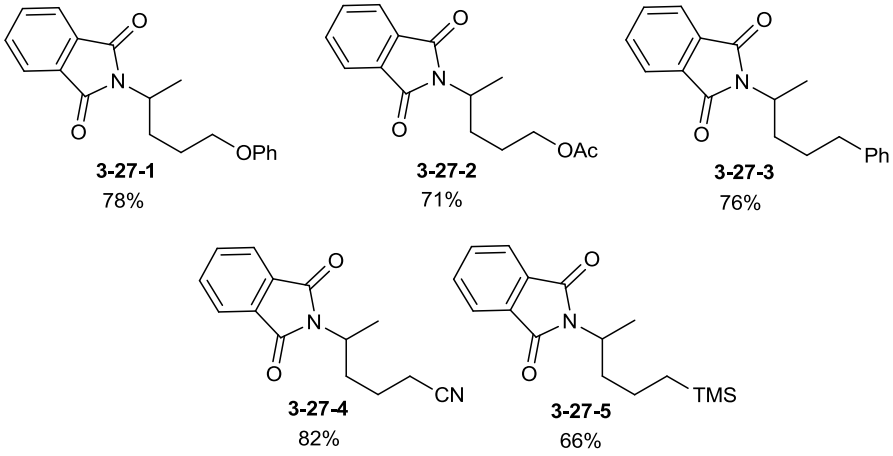
Scheme 3.24 The preparation of xanthate **3-27**

As we expected, the addition of **3-27** to olefins gave adducts in high yield and only10-15 mol% DLP was required for complete conversion. To compare the difference between xanthate **BQS-12** and **3-27**, the addition of **3-27** to allylacetate was examined (Scheme 3.25). The yield was 81% compared with 88% using xanthate **BQS-12** under the same conditions. There was therefore no apparent difference as far as yields were concealed. However, in the case of xanthate **BQS-12** only 5 mol% of DLP was needed to complete the reaction but 10 mol% DLP for xanthate **3-27**. A possible explanation might be attributed to the steric effect which would lower the efficiency of radical addition step.



Scheme 3.25 Radical addition of xanthates **BQS-12** and **3-27** to allyl acetate

As shown in Scheme 3.26, we have also tested the radical addition of xanthate **3-27** to other olefins such as 4-allylanisole, allylbenzene, allylcyanide and allyltrimethylsilane.

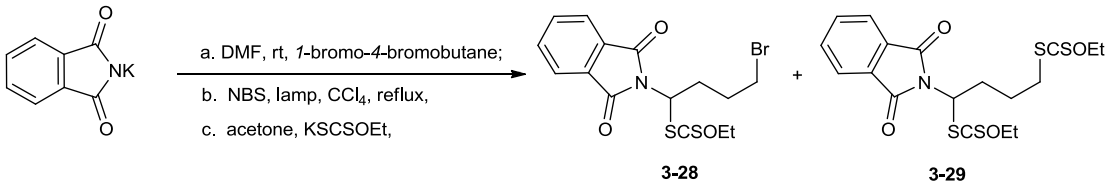


Scheme 3.26 *N*-phthalimide protected alkyamines

3. Radical synthesis of chloroalkylamines and pyrrolidines

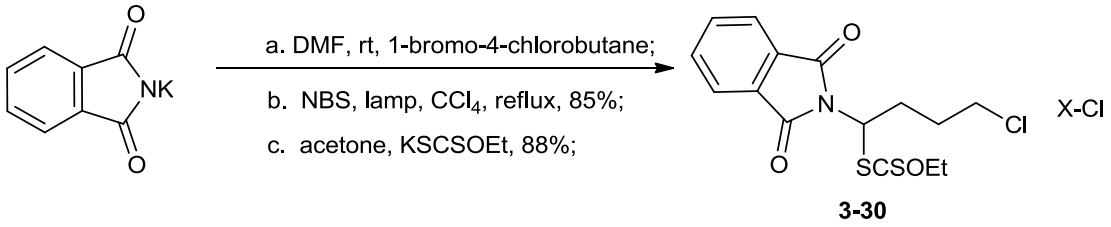
1,4-Dibromobutane was next employed to prepare the corresponding xanthate. The replacement of bromine by potassium ethyl xanthate led to the formation of xanthate **3-28**, but a small amount of byproduct **3-29** was also observed, even when

using less than one equivalent of the xanthate salt (Scheme 3.27). Although xanthate **3-28** was the major product, it couldn't be separated from the mixture. Therefore, the mixture of xanthate **3-28** and byproduct **3-29** was used directly for the radical addition to olefins. 50 mol% DLP was required to totally consume the starting material but, instead of the desired adduct, only an undetermined mixture and a small amount of the reduced product were observed.



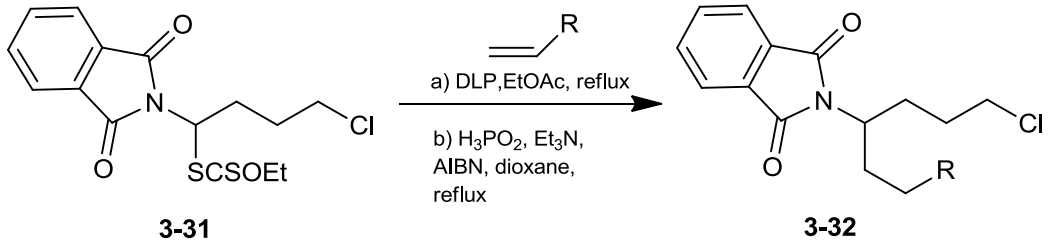
Scheme 3.27 Synthesis of xanthate **3-28**

Since even trace amounts of impurity such as **3-29** might prevent the radical chain process, we reexamined this process by replacing 1,4-dibromobutane by 1-bromo-4-chlorobutane (Scheme 3.28). 0.9 Equivalent of potassium O-ethyl xanthate was used, and only the desired xanthate **3-30** was obtained.



Scheme 3.28 Synthesis of xanthate **3-30**

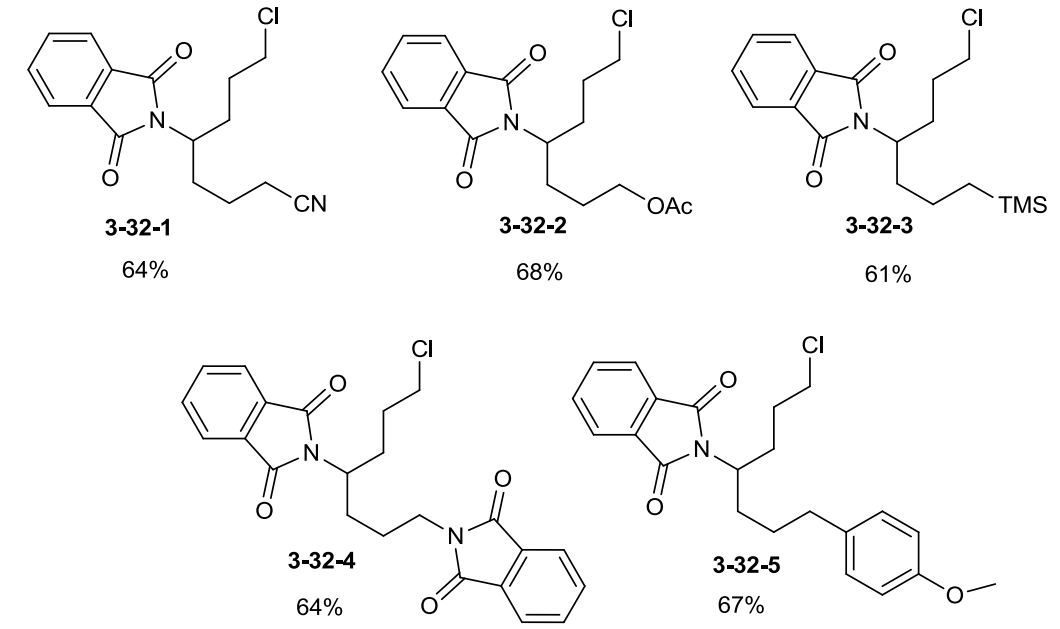
To our delight, the addition of xanthate **3-30** to various olefins gave the desired adducts. Next, the xanthate was reduced off by action of the triethylammonium salt of hypophosphorus acid to afford the corresponding phthalimides **3-32** in generally good yields (Scheme 3.29).



3-31 **3-32**

Scheme 3.29 Synthesis of **3-32**

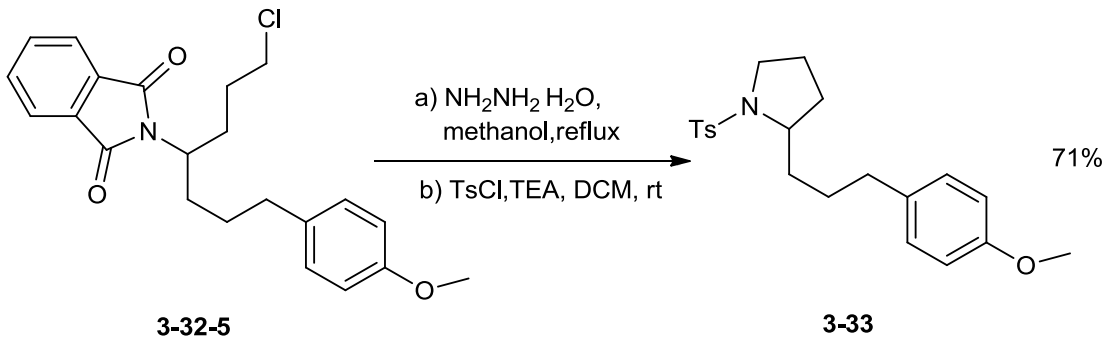
Besides the various functional groups that are incorporated into these products, the presence of the chlorine atom four carbons away in these adducts is especially useful for the construction of heterocyclic rings or for other extensions through the intermolecular substitutions (Scheme 3.30).



Scheme 3.30 *N*-phthalimide protected chloroalkylamine **3-32**

We have illustrated one such possibility in the case of **3-32-5** as shown in Scheme 3.31. To unmask the amine, we added hydrazine hydrate to a refluxing methanol solution of **3-32-5**, and this treatment furnished the corresponding cyclopentylamine directly. After concentration of the solution, the residue was dissolved in DCM without purification followed by addition of triethylamine and 4-toluenesulfonyl chloride in a 1:1 ratio. This afforded the easy to isolate derivative

3-33 in 71% yield for the two steps. Therefore, this concise and highly efficient route can be exploited to construct substituted pyrrolidines, especially by modification at their position 2.[103]



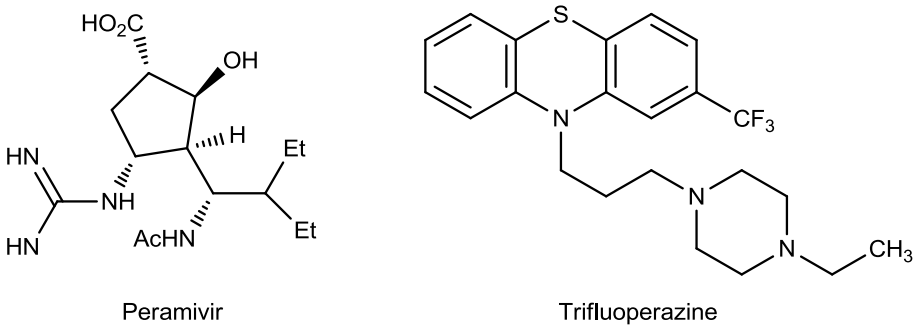
Scheme 3.31 Synthesis of pyrrolidines **3-33**

4. Radical synthesis of 1,3-diamines and polyamines

4.1. 1,3-diamines

1,3-diamines are highly versatile species, which have been used in acid-base catalysis, as molecular recognition devices, as metal-chelating moieties, and as functional group in the synthesis of macrocycles and other larger molecular.[104] As shown in Figure 3.2, peramivir is an antiviral drug developed by BioCryst Pharmaceuticals, Inc. for the treatment of influenza;[105] trifluoperazine has been used for patients with behavioural problems, severe nausea and vomiting, and its activity is attributed to its central antiadrenergic, antidopaminergic, and minimal anticholinergic effects.[106] Furthermore, there have been numerous applications of chiral 1,3-diamines as chiral auxiliaries, chiral catalysts and chiral ligands in enantioselective synthesis.

[103] (a) Enders, D.; Goddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863. (b) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (c) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400.
[104] Bender, J.; Meanwell, N. A.; Wang, T. *Tetrahedron* **2002**, *58*, 3111.
[105] Shetty, A. K.; Peek, L. A. *Expert Rev. Anti Infect. Ther.* **2012**, *10*, 123.
[106] Post, A.; Warren, R. J.; Zarembo, J. E. *Anal. Profiles Drug Subst.* **1980**, *9*, 543.



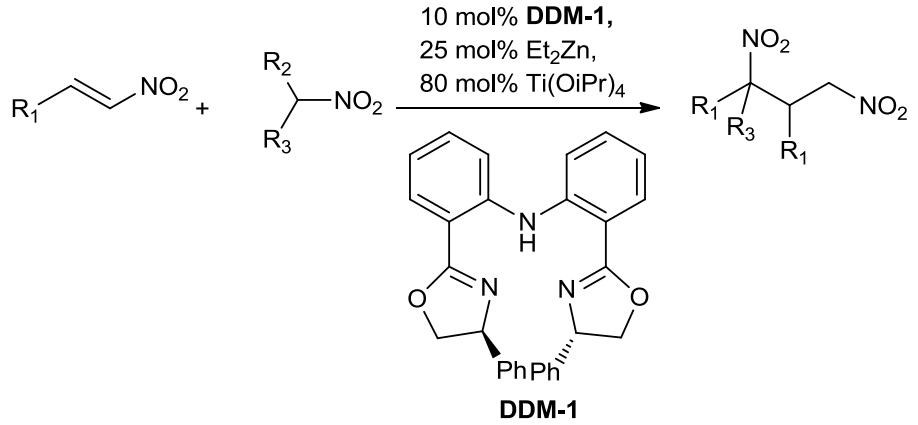
Peramivir Trifluoperazine

Figure 3.2 Examples of pharmaceutical products

4.2. Synthesis of 1,3-diamines

4.2.1. Reduction of 1,3-dinitro compounds to 1,3-diamines

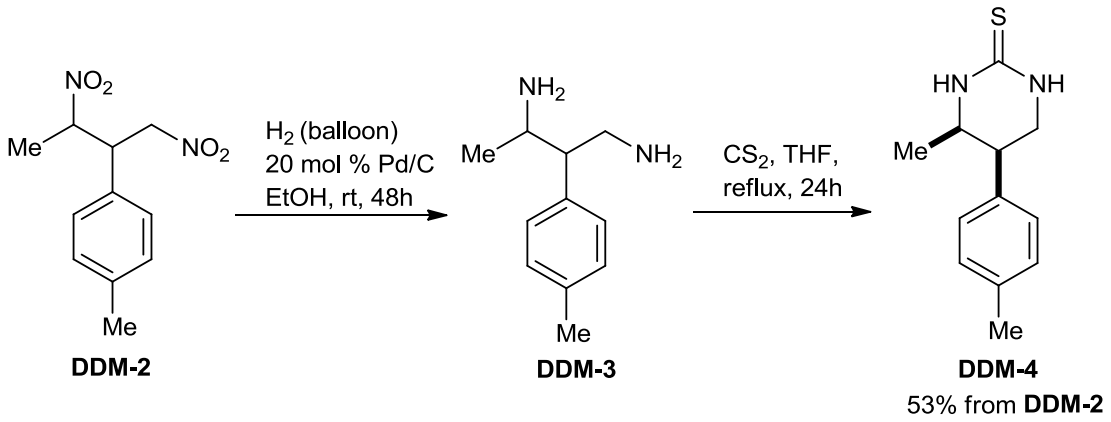
An investigation undertaken by Du and co-workers disclosed that the bis(oxazoline) ligand such as **DDM-1** or bis(thiazoline) ligand would promote the Zn (II)-catalyzed stereoselective addition of nitroalkanes to a wide range of nitroalkenes, in a highly stereoselective approach to 1,3-nitroamines (Scheme 3.32).[107]



Scheme 3.32 Synthesis of 1,3-nitroamines

Like the example shown in Scheme 3.33, these 1,3-dinitroalkanes **DDM-2** can be converted into the corresponding enantioenriched 1,3-diamines **DDM-3** via simple reduction of their nitro groups.

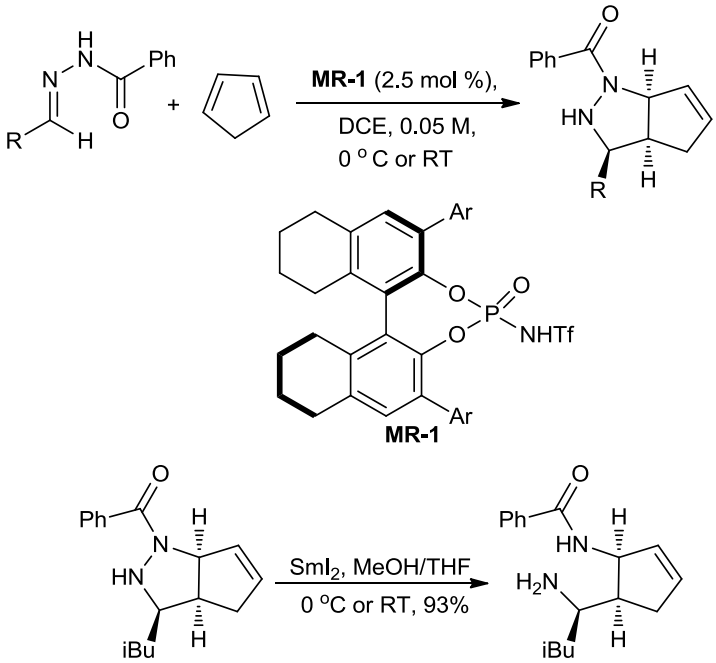
[107] Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.



Scheme 3.33 Reduction of 1,3-dinitroalkanes

4.2.2. 1,3-Diamines from pyrazolidine derivatives

Rueping and co-workers developed a general and highly enantioselective approach to access optically active pyrazolidine derivatives.[108] As shown in Scheme 3.34, the cycloaddition occurred between various alkenes and *N*-benzoylhydrazones and was catalyzed by Bronsted acid **MR-1**. Cleavage of the N-N bond provided the corresponding 1,3-diamines in high yield.

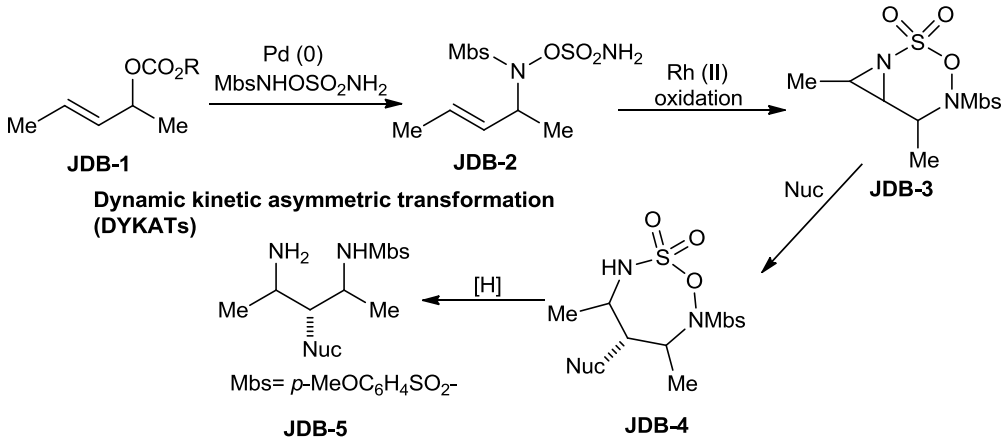


Scheme 3.34 Synthesis of 1,3-diamines from pyrazolidine derivatives

[108] Rueping, M.; Maji, M. S.; Kucuk, H. B.; Atodiresei, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 12864.

4.2.3. Asymmetric synthesis of diamine derivatives based on organocatalysis

Recently Trost and co-workers described a route to 1,3-diamines involving a rhodium catalyzed cyclization step (Scheme 3.35).[109] Palladium-catalyzed allylic amination of **JDB-1** gave the allylic hydroxylamine-derived sulfamate esters **JDB-2** via a dynamic kinetic asymmetric transformation. Intermediate **JDB-2** was then subjected to a rhodium catalyzed intramolecular amination process to afford aziridine **JDB-3**. Finally, ring opening of the latter furnished compound **JDB-4,** which was reduced to afford the corresponding 1,3-diamine **JDB-5**.



Scheme 3.35 Synthesis of diamine based on rhodium catalyzed proccess

4.3. Xanthate chemistry based approach to access 1,3-diamines

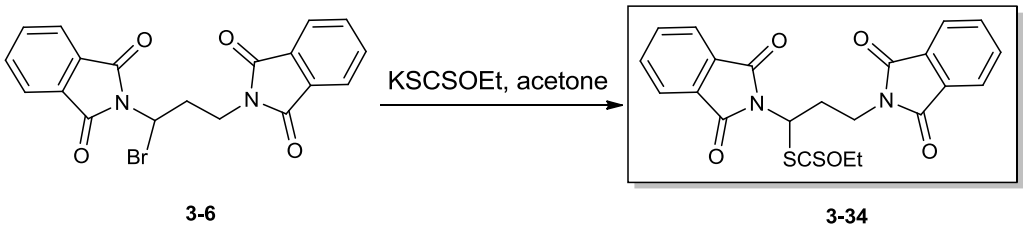
Although numerous methods to access 1,3-diamines have been reported, due to their broad applications in organic synthesis and medicinal chemistry, there has remained an interest in investigating other synthetic routes, especially modular approaches and metal free methods.

4.3.1. Radical synthesis of 1,3-diamines using xanthate **3-34**

As we mentioned in chapter 2, the synthesis of 1,4- and 1,5-diamines was developed in our group based on the decarbonylation of α-amino acid to prepare the

[109] Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190.

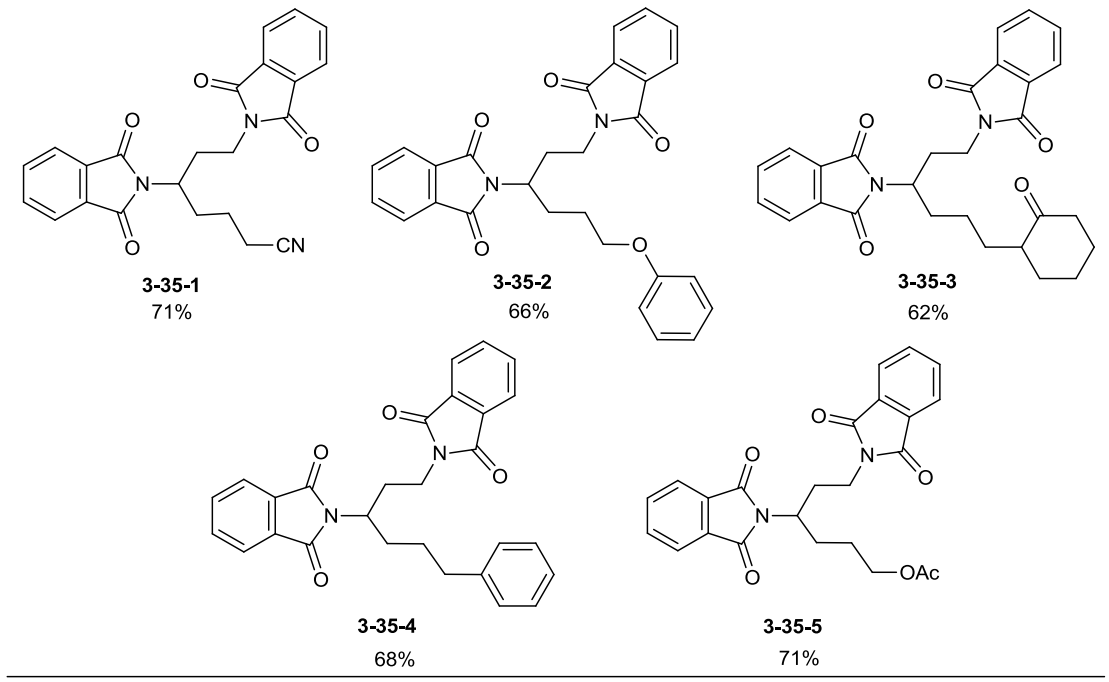
corresponding xanthates. However, 2,4-diaminobutanoic acid as the starting material for synthesis of 1,3-diamine is much more expensive in comparison with starting with 1,3-diaminopropane via the bromination reaction. We thus converted 1,3-diaminopropane into xanthate **3-34** in nearly quantitative yield (Scheme 3.36).



3-6 **3-34**

Scheme 3.36 Synthesis of xanthate **3-34**

The addition of xanthate **3-34** to several unactivated olefins proceeded in generally high yield needing 10-15 mol% DLP for completion. The examples are collected in Scheme 3.37. As before, these adducts were reduced by the Barton reagent to give compound **3-35** bearing various side chains in a total yield ranging from 62% to 71%.

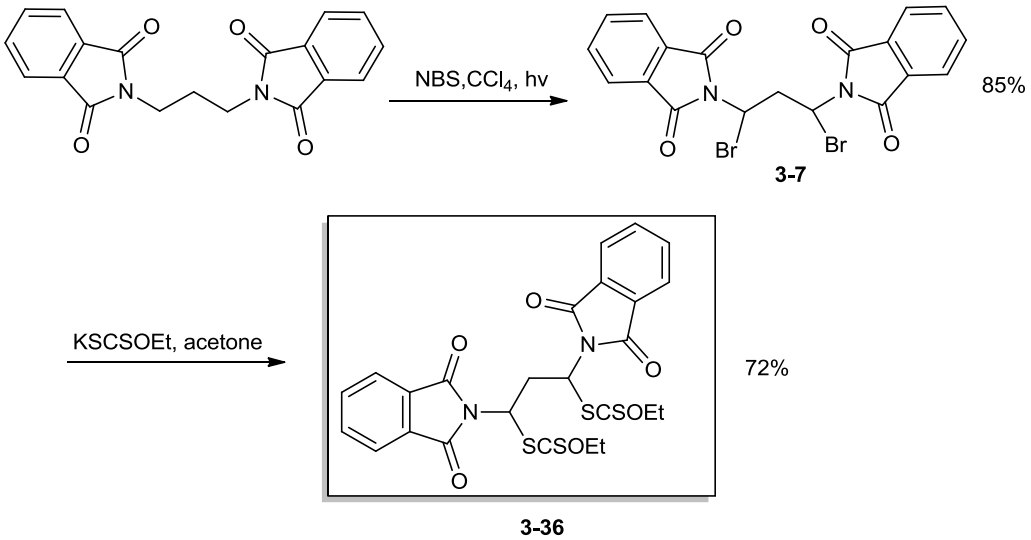


3-35-1 71%
3-35-2 66%
3-35-3 62%
3-35-4 68%
3-35-5 71%

Scheme 3.37 Examples of 1,3-diamines **3-35**

4.3.2. Radical synthesis of 1,3-diamines by using xanthate **3-36**

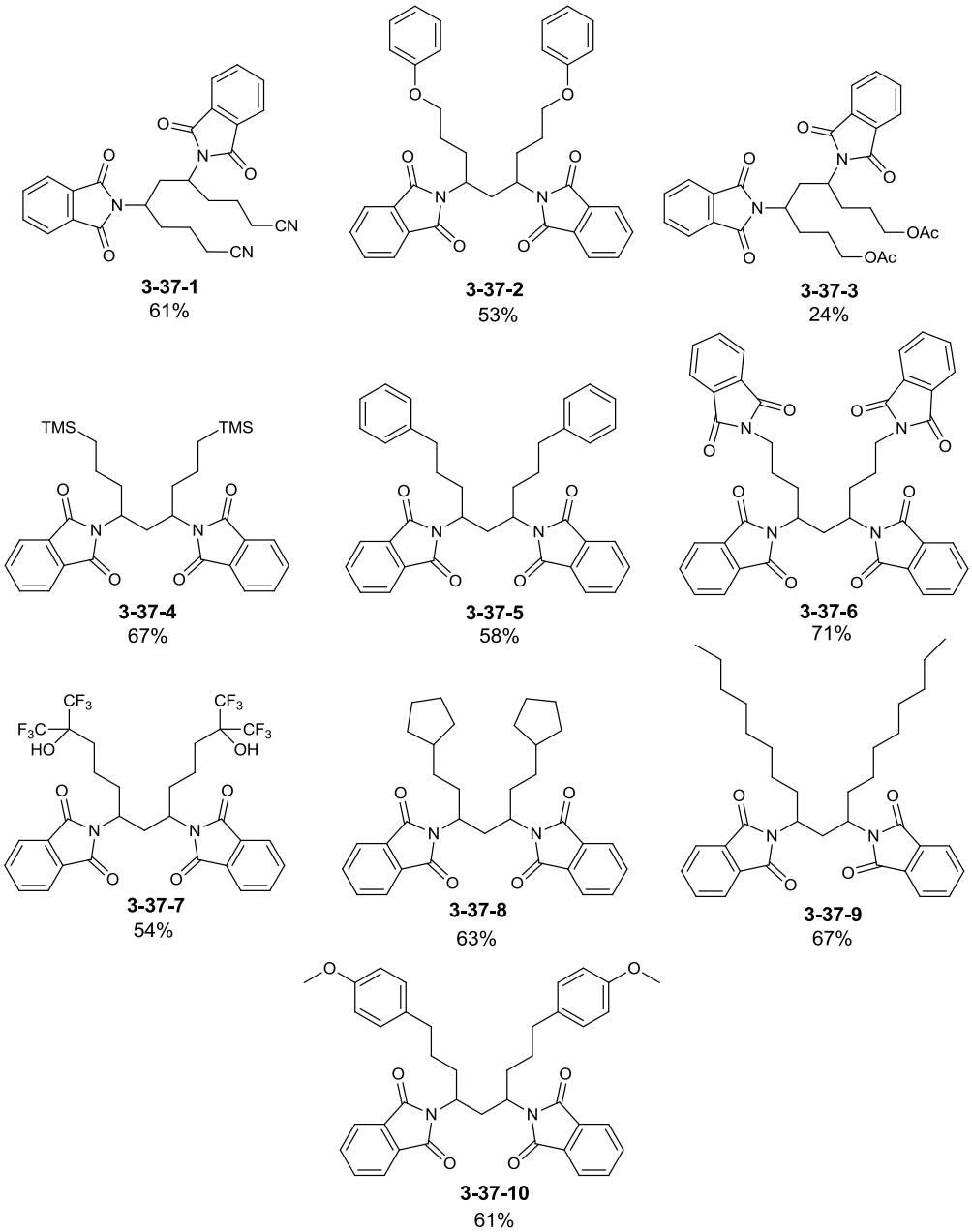
Adding more than one equivalent of *N*-bromosuccinimide with respect to the substrate, a small amount of dibrominated product was formed in the mixture. Thus, we repeated this process by adding two equivalents of *N*-bromosuccinimide and obtained dibrominated product **3-7** along with a small amount of monobrominated product **3-6**. To secure the total transformation of **3-5** into **3-7**, 2.5 equivalents of *N*-bromosuccinimide were needed. Replacement of the bromine by the xanthate group furnished xanthate **3-36** in quantitative yield (Scheme 3.38). The radical addition of xanthate **3-36** to various olefins was then investigated and the corresponding double addition products were observed. Usually, but depending on the boiling points of olefins more than one equivalent or even four equivalents olefins were added to accomplish a complete transformation. We found it was quite difficult to control the radical addition to afford only mono-addition products. The double addition products from xanthate **3-36** are particularly interesting. Reductive removal of the xanthate groups simplified considerably the mixture, since now only *meso* and *dl* modifications of these diamines remained in approximately 2:1 ratio.



Scheme 3.38 Synthesis of xanthate **3-36**

The examples displayed in Scheme 3.39 give an idea of the scope and the

tolerance for the various functional groups.To best of our knowledge, this is the first bidirectional approach to access 1,3-disubstituted diaminopropanes with a C_{2v} symmetry. It is worthwhile noting that tetramine **3-37-6** is synthesized in two steps. Such compounds are difficult to obtain by current methods. In the case of **3-37-7**, four trifluoromethyl groups are incorporated into the *N*-phthalimide protected diamine.



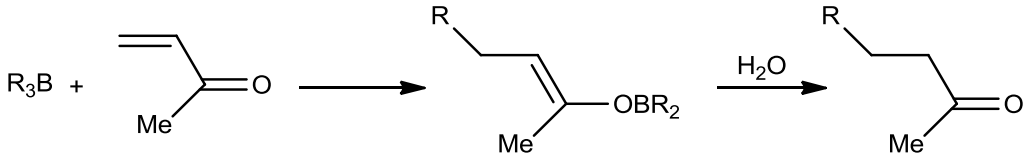
Scheme 3.39 Examples of **3-37**

5. Radical synthesis of amines involving the autoxidation of triethylborane

5.1. Organoboranes

Brown received the Noble Prize in chemistry in 1979 for his pioneering research on the applications of organoborane compounds in organic synthesis. In the following decades, due to the rich and varied chemistry of organoboranes, there has been an enormous increase in the applications of organoboranes in organic synthesis.

The first organoborane induced radical reactions were reported in 1967. Brown and co-workers found that trialkylboranes underwent 1,4-conjugate addition with unsaturated ketones followed by hydrolysis to furnish the corresponding ketones (Scheme 3.40). However, they did not immediately realize that it was a free radical process until they found that a small amount of oxygen in the nitrogen gas was the key to a successful addition.[110]



Scheme 3.40 1,4-conjugate addition of trialkylboranes to unsaturated ketones

Later, the use of boron alkyls in combination with oxygen was developed by Oshima and co-workers and experienced a fast growth in interest and popularity.[111] In 2001, Ollivier and Renaud described many applications of boron alkyls in free radical initiated syntheses and discussed the now accepted mechanism for the autoxidation of organoboranes in their review.[112]

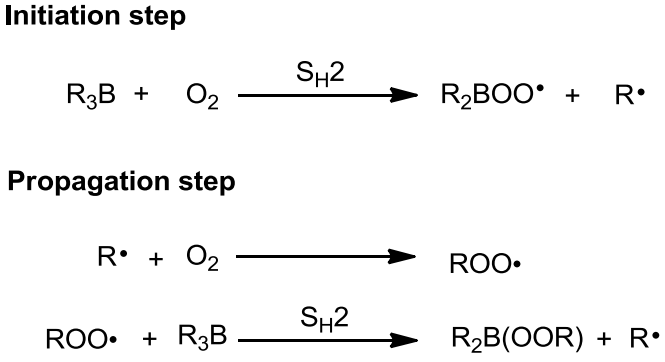
As shown in Scheme 3.41, in the initiation step, trialkylborane liberates a free alkyl radical upon exposure even to trace amounts of oxygen. In the propagation step, this free alkyl radical combines with another molecule of oxygen to generate a peroxy

[110] (a) Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H. C.; Rogic, M. M.; Rathke, M. W.; *J. Am. Chem. Soc.* **1967**, *89*, 5708. (b) Brown, H. C.; Midland, M. M. *Angew. Chem. Int. Ed.* **1972**, *11*, 692.

[111] Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.

[112] Ollivier, C.; Renaud, P.; *Chem. Rev.* **2001**, *121*, 3543.

radical which is readily captured by trialkylboranes to generate another alkyl radical, and so on.

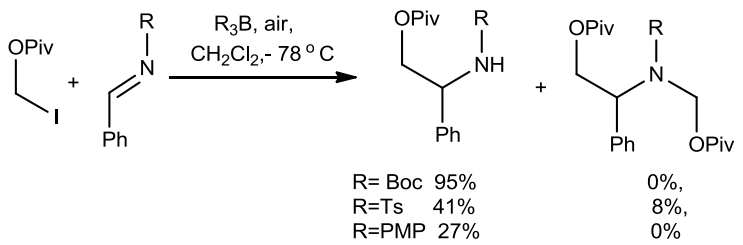


Scheme 3.41 Autoxidation of organoborane

5.2. Applications of organoborane in radical synthesis

Currently, organoboranes have been applied to a wide range of free-radical reactions, such as additions to alkynes, alkenes, ethynyloxiranes, azidoalkenes and imines or conjugate addition to unsaturated ketones and aldehydes or hydroxylation, azidation and halogenation.[113]

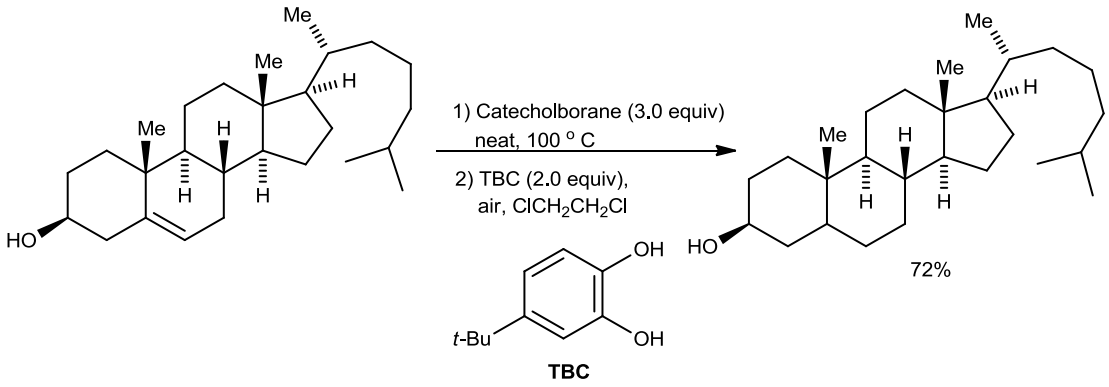
Recently, Yamada and co-workers described a triethylborane-induced tin-free radical alkylation of *N*-protected imines with iodomethylpivalate to give the corresponding amine products (Scheme 3.42).[114] Since the autoxidation of triethylborane with a small amount of oxygen proceeds smoothly even at -78 ℃, this reaction could be completed at low temperature (-78 to -20 ℃), a great advantage when using triethylborane-air as the initiator.



Scheme 3.42 Triethylborane-induced radical alkylation of *N*-protected imines

[113] Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71.
[114] Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 1547.

The conversion of alkenes to alkanes relies mainly on metal catalyzed hydrogenation. Recently, Renaud and co-workers reported the reduction of alkylboron compounds with catechols via a radical chain process (Scheme 3.43).[115] The hydroboration of the alkene gives the *B*-alkycatecholborane intermediate and then by using catechols as the reducing agent *B*-alkycatecholborane is reduced to form corresponding alkane in the presence of air via a free radical chain process.

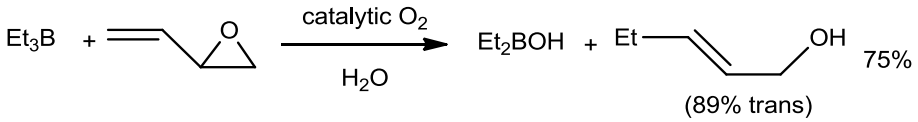


Scheme 3.43 Reduction of alkylboron compounds with catechols

5.3. Organoboranes in combination with xanthate chemistry

5.3.1. Radical addition of trialkyboranes to 1,3-butadiene monoxide

In 1971, Brown and co-workers initially reported the addition of trialkyboranes to 1,3-butadiene monoxide in the presence of trace amounts of oxygen via a free radical chain process (Scheme 3.44).[116]

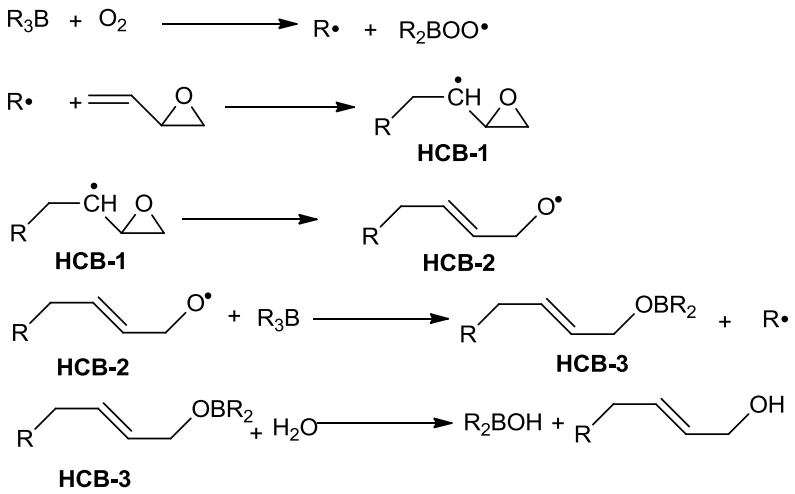


Scheme 3.44 Addition of trialkyboranes to 1,3-butadiene monoxide

A plausible mechanism of this radical process is outlined in Scheme 3.45. The autoxidation of trialkyborane gives an alkyl radical which adds to the double bond to

[115] Villa, G.; Povie, G.; Renaud, P. *J. Am. Chem. Soc.* **2011**, *133*, 5913.
[116] Suzuki, A.; Miyaura, N.; Itoh, M.; Brown, H. C.; Holland, G.W.; Negishi, E. Rogic, *J. Am. Chem. Soc.* **1971**, *93*, 2792.

generate a radical intermediate **HCB-1**. The opening of the epoxide ring leads to another radical intermediate **HCB-2** which is readily trapped by trialkyborane to generate intermediate **HCB-3** and another alkyl radical. Finally, the hydrolysis of intermediate **HCB-3** provides the corresponding allylic alcohol products.

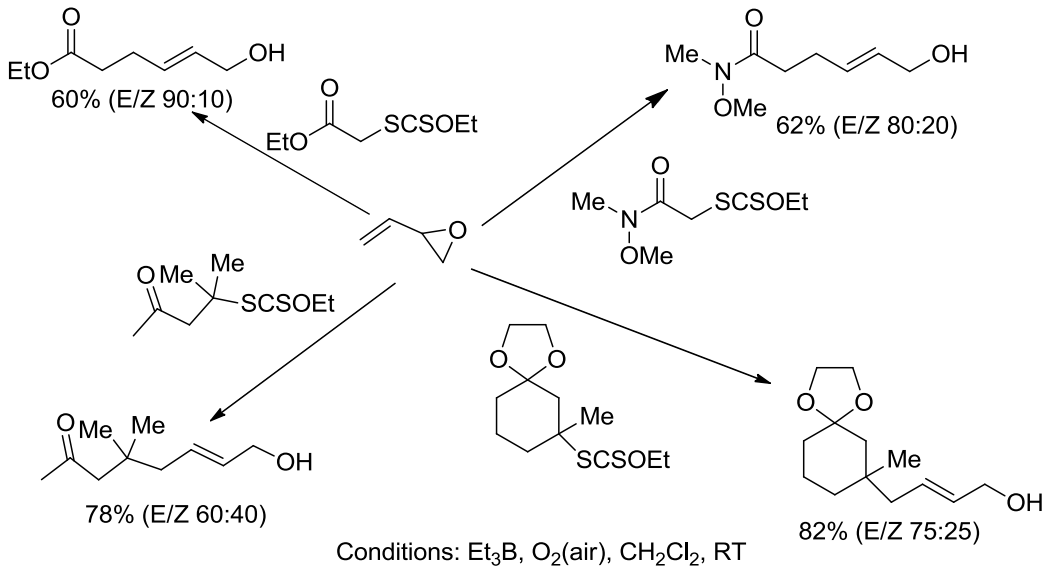


Scheme 3.45

5.3.2. Radical additions of xanthates to vinyl epoxides and related derivatives

The radical addition of xanthate to vinyl epoxides using triethylborane-air as the radical initiator was accomplished in our group.[117] As illustrated in Scheme 3.46, the addition of various xanthates to butadiene monoepoxide gave the corresponding allylic alcohols bearing a wide range of functional groups.

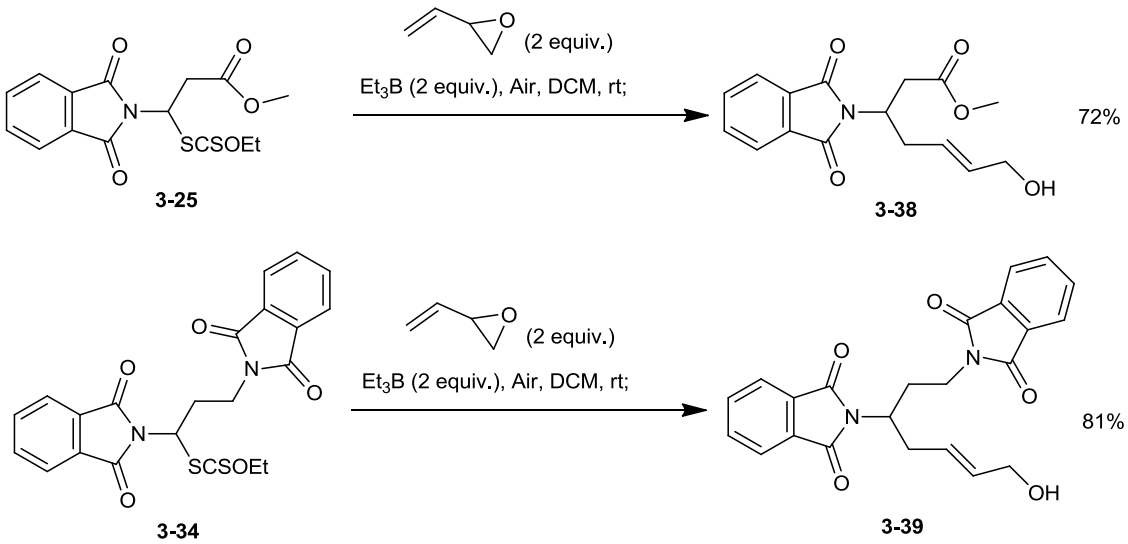
[117] Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem. Int. Ed. Eng.* **2006**, *45*, 6520.



Scheme 3.46 Addition of various xanthates to butadiene monoepoxide

5.3.3. Radical synthesis of cyclic diamines

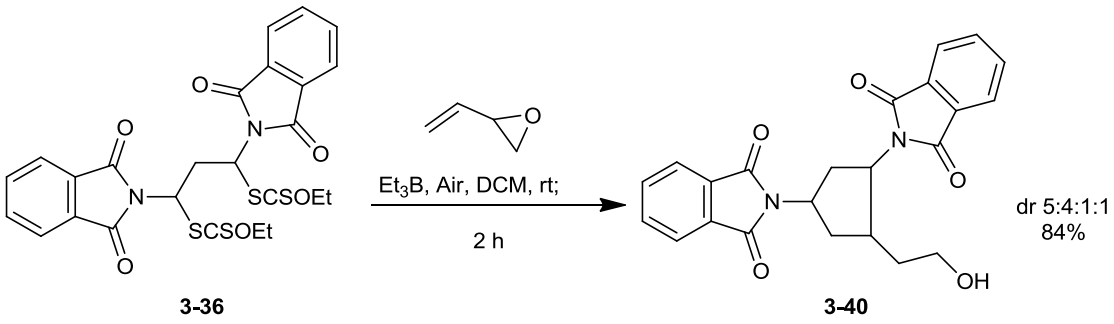
Based on this previous study, we tested the addition of xanthates **3-25** and **3-34** to butadiene monoepoxide via the same approach. The desired products **3-38** and **3-39** were obtained in high yield within two hours (Scheme 3.47).



Scheme 3.47 Radical addition of xanthate **3-25** and **3-34** to butadiene monoepoxide

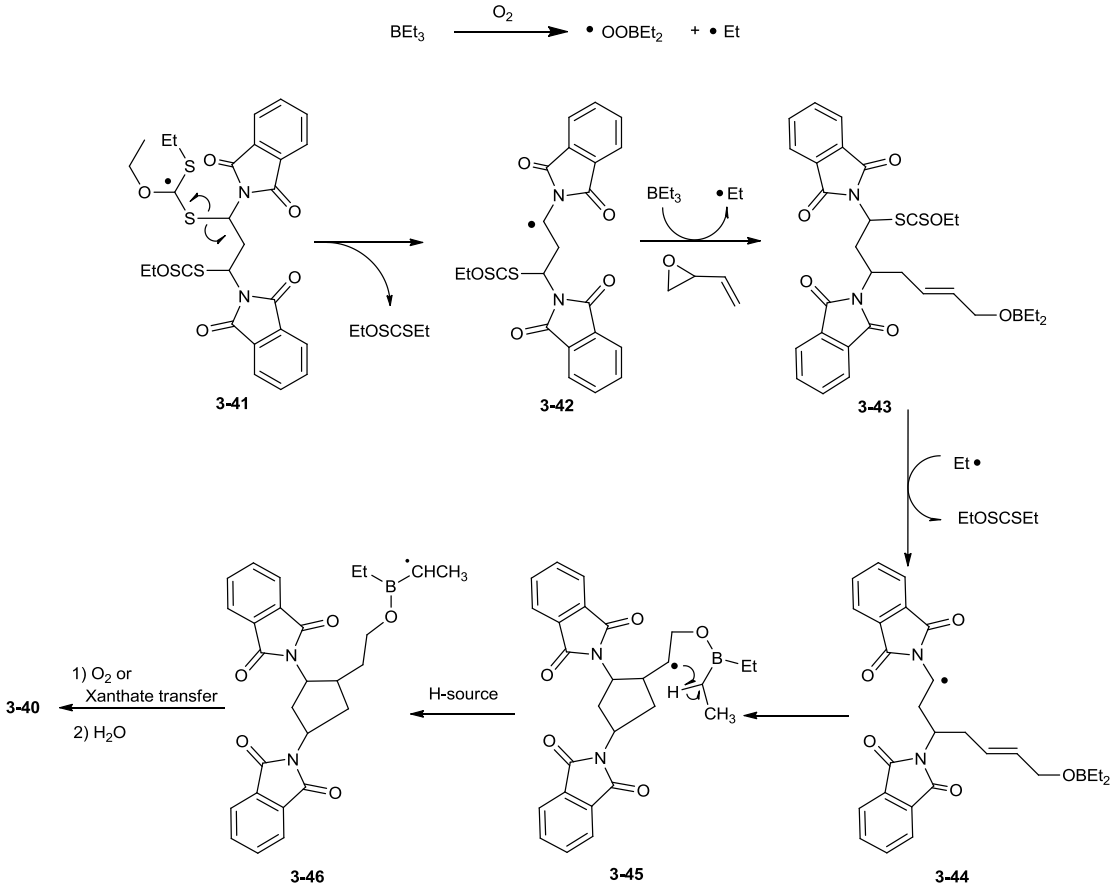
It should be more interesting to apply this protocol for the synthesis of cyclopentane-1,3-diamine derivatives such as **3-40** by using xanthate **3-36**, which may undergo an intermolecular addition followed by a cyclization step. Surprisingly,

radical reaction between xanthate **3-36** with butadiene monoepoxide quickly gave the cyclized reduced product directly in 84% yield (Scheme 3.48).



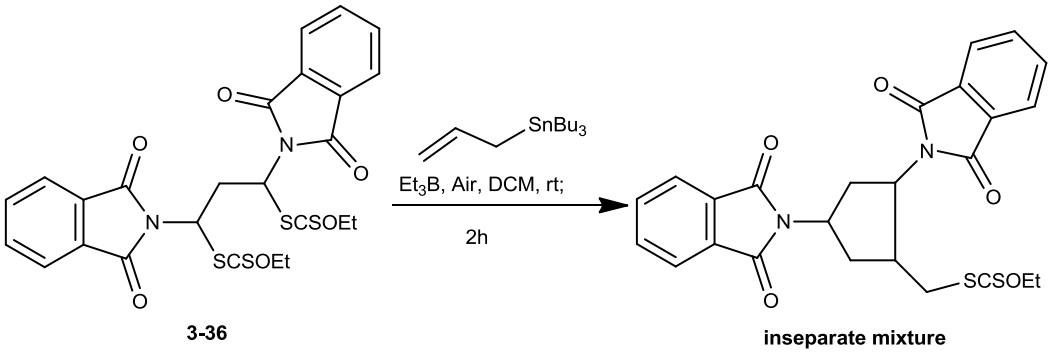
Scheme 3.48 Radical addition of xanthate **3-36** to butadiene monoepoxide

A plausible mechanism is proposed in Scheme 3.49. The autoxidation of triethylborane generates an ethyl radical which adds to the xanthate to give intermediate **3-41**. This then collapses to radical **3-42**, which is readily trapped by the butadiene monoepoxide to form a ring opened product **3-43** and another ethyl radical which ultimately exchanges the xanthate group to form radical intermediate **3-44**. The cyclization of the latter leads to **3-45** which then abstracts a hydrogen α to the boron. The resulting radical **3-46** either readily reacts with oxygen or exchanges a xanthate group. In either case, hydrolysis finally leads to the observed alcohol **3-40**. Radical **3-46** is stabilized by delocalization into the empty orbital on boron.



Scheme 3.49 Mechanism of radical addition between xanthate **3-36** and butadiene--monoepoxide

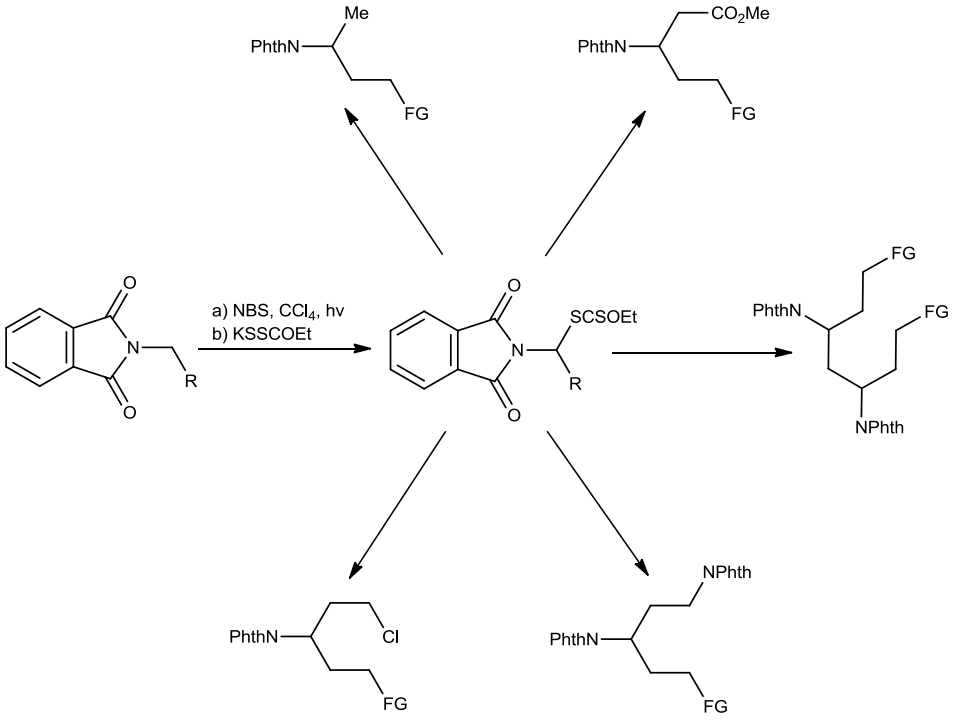
We expected that a similar radical reaction would occur between xanthate **3-36** and allyltributylstannane. Over the same period xanthate **3-36** was totally consumed, but only an inseparable mixture was obtained (Scheme 3.50). Therefore, it was difficult to tell what exactly occurred during this radical process from the NMR spectrum of the crude mixture.



Scheme 3.50 Addition of xanthate **3-36** to allyltributylstannane

Conclusion

In conclusion, this radical hydroaminomethylation process is based on an increasing stabilising effect provided by the phthalimido group. In previous studies, we have applied this feature to the synthesis of other amine derivatives, such as *β*-lactams, 1,4- and 1,5-diamines, *γ*-amino acids, *β*-aminoalcohols, 2-aminotetralines and triamines. In this study, by exploiting yet another radical reaction, the classical Wohl-Ziegler allylic bromination, the bromination of *N*-phthalimide protected amines has significantly extended the scope of this radical hydroaminoalkylation method. These novel xanthates derived from easily accessible primary amines have proved to be powerful tools for the preparation of *β*-aminoacids, alkylamines, 1,3-diamines and polyamines (Scheme 3.51). The present approach, in association with those of the previous studies, constitutes an extremely powerful, general and modular strategy for the fast preparation of highly functionalised amines.



Scheme 3.51

Chapter 4

Radical Synthesis of 1,2-Diamines

Introduction

Vicinal diamines represent indispensable structural motifs in many natural and bioactive compounds. Some pharmaceutically interesting substances are presented in Figure 4.1. Massadine is one of the few described inhibitors of geranylgeranyl--transferase type I (GGTase I), which was isolated from the marine sponge Stylissa aff.[118] (-)-Agelastatin A is a naturally occurring oroidin alkaloid with powerful antitumor activity. It inhibits cancer cell proliferation by causing cells to accumulate in the G2 phase of cell cycle.[119] Penicillins, a group of hugely important antibiotics, are still widely used today. Their discoveries date back to 1928 to the famous work of the Scottish scientist and Nobel laureate A. Fleming.[120] Biotin, also known as vitamin H, is essential in fatty acid biosynthesis, branched-chain amino acid catabolism, and gluconeogenesis.[121] Synthetic 1,2-diamines have also proved of some importance. Thus, Tamiflu is an antiviral widely utilized to prevent or slow down the spread of flu virus between cells in the body;[122] A-315675, [123] a novel trisubstituted pyrrolidine carboxylic acid, is a highly potent inhibitor of influenza neuraminidase and has been synthesized by several groups; Oxaliplatin[124] (Eloxatin; Sanofi-Synthelabo), the first platinum-based antineoplastic agent, used to treat cancer, was discovered in 1976 at Nagoya City University by professor Kidani; Diazepam, a benzodiazepine drug, is used to treat anxiety, panic attacks, insomnia.[125]

---

[118] Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W.; Fusetani, N. *Org. Lett.*, **2003,** *5*, 2255.

[119] (a) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012,** *134*. 7516. (b) Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. *Mol. Canc. Therapeu.* **2008,** *7*, 548.

[120] Nicolaou, K.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993.

[121] Jestin, E.; Moreau, F.; Florentin, D.; Marquet, A. *Bioorg. Med. Chem.* **1996,** *4*, 1065.

[122] Burch, J.; Corbett, M.; Stock, C.; Nicholson,K.; Elliot, A. J.; Duffy, S.; Westwood, M.; Stephen, P.; Lesley, S. *Lancet Infect Dis* 2009, 9, 537.

[123] Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716.

[124] Wheate, N. J.; Walker, S.; Craig, G. E.; Oun, R. *Dalton Trans.*, **2010**, *39*, 8113.

[125] Ravenell, R.; Neugebauer, N. M.; Niedzielak, T.; Donaldson, S. T. *Behav Brain Res.*, **2004**, *270*, 68.

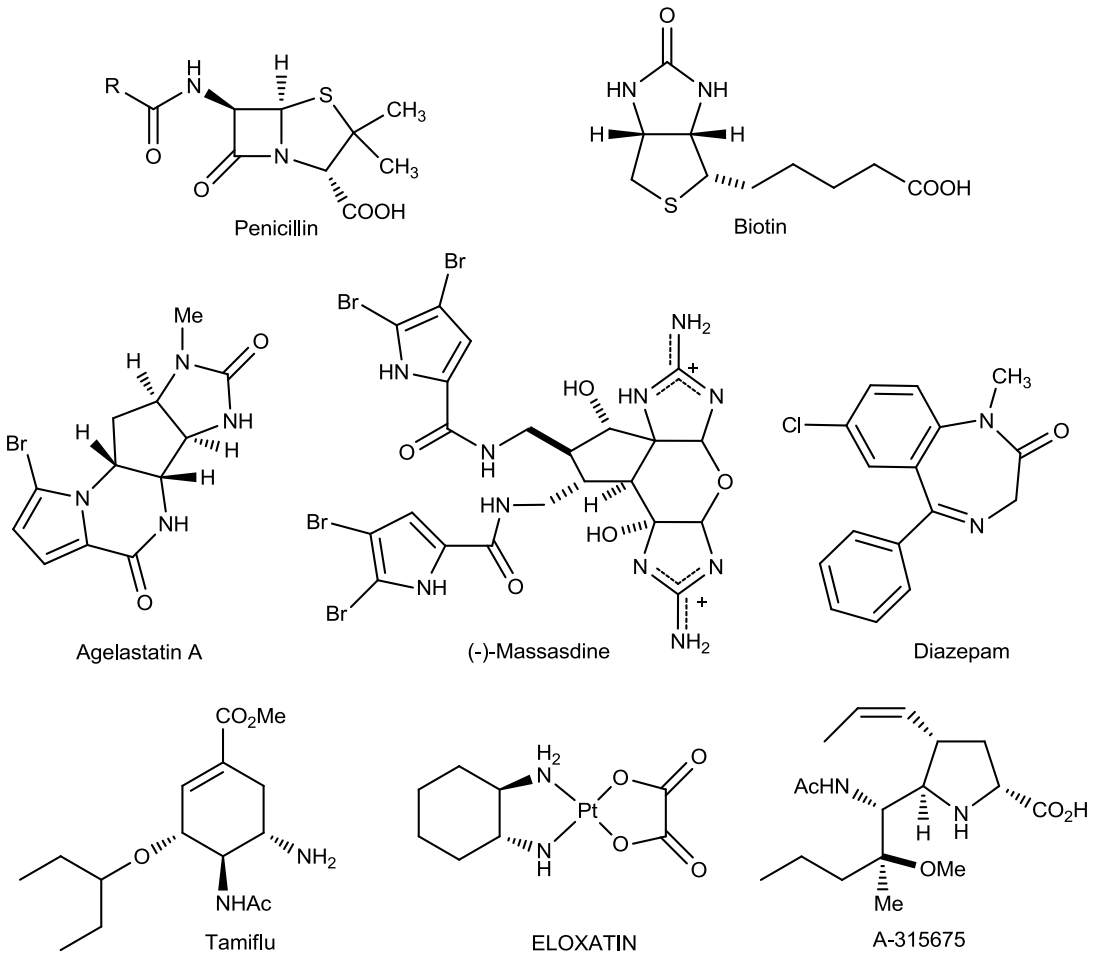


Figure 4.1 Structures of some pharmaceutical interesting compounds

Due to the highly valuable medicinal applications of diamines, there has been a great interest in their preparation. We therefore directed our studies on the degenerative transfer of xanthates towards the construction of highly functionalized diamines. Our results will be described in this chapter.

I. Preparation of 1,2-diamines and their applications in organic synthesis

1. Preparation of 1,2-diamines

A plethora of methods to access diverse 1,2-diamines have been developed in the past decades.[126] In the following paragraphs, a few of the more well-known strategies for the synthesis of 1,2-diamines, such as diamination of alkenes, ring-opening reactions of aziridines, reductive coupling of imines and classical named reactions such as the Mannich reaction and the aza-Cope rearrangement will be briefly introduced.

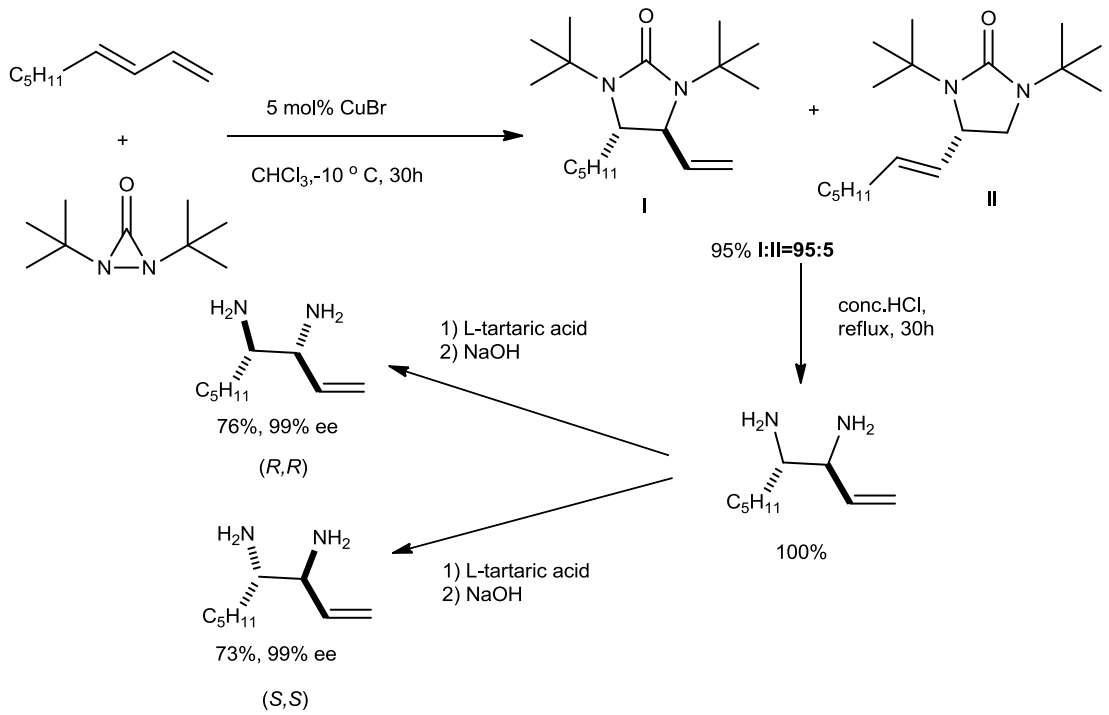
1.1. Diamination of alkenes

Diamination of olefins is an effective and concise strategy to synthesize vicinal diamine. It has been intensively studied and reported; however, especially for internal alkenes, accomplishing this difunctionalization with high chemo-, regio- and diastereoselectivity remains a significant challenge. Among various metal-catalyzed diamination protocols, one powerful Cu (I)-catalyzed regioselective diamination of conjugated dienes was developed by Shi and co-workers.[127] As shown in Scheme 4.1, various dienes could be regioselectively diaminated by using di-*tert*-butyldiaziridinone as the nitrogen source. This Cu (I)-catalyzed diamination can be accomplished in good yield even on a large scale.

---

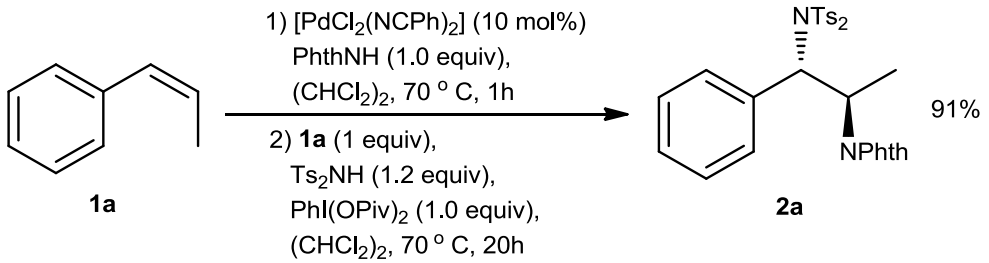
[126] (a) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887. (b) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516. (c) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.*, **2004**, *6*, 2397. (d) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (e) Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* **2003**, 9, 5581. (f) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (g) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184. (h) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, *6*, 4747. (i) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, 6, 3953. (j) Mercer, G. J.; Sigman, M. S. *Org. Lett.*, **2003**, *5*, 1591.

[127] (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Zhao, B.; Peng, X.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2012**, *132*, 11009.



Scheme 4.1 Copper-catalyzed diamination of alkenes

Recently, another study on the diamination of (Z)-*β*-methylstyrene based on a palladium (II/IV) catalyzed process was reported by Muniz and co-workers (Scheme 4.2). Phthalimide and bistosylimide as the nitrogen source were incorporated into (Z)-*β*-methylstyrene.[128] This highly chemo-, regio- and diastereoselective reaction can afford the corresponding diamine products on a 17 mmol scale, which is difficult to accomplish by traditional methods.



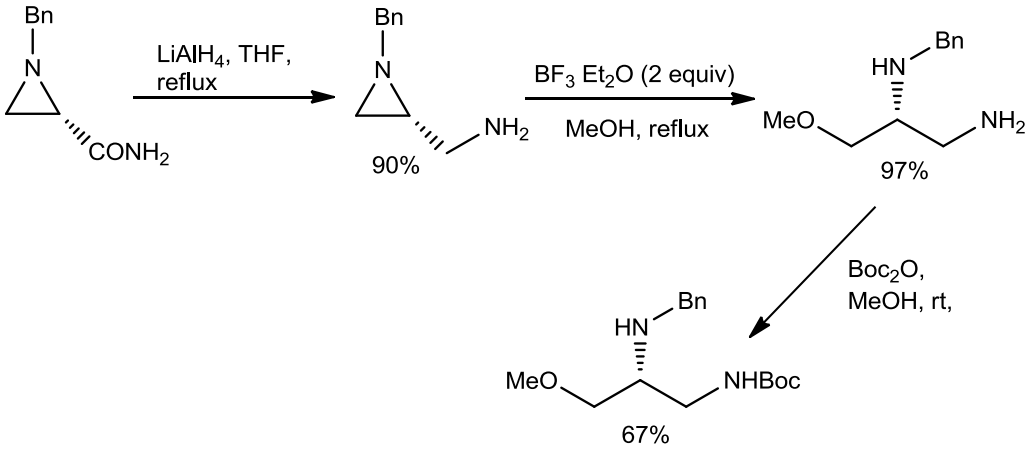
Scheme 4.2 Palladium catalyzed diamination of (Z)-*β*-methylstyrene

[128] Mart ńez, C.; Muniz, K. *Angew. Chem. Int. Ed.* **2012,** *51*, 7031.

1.2. Ring-opening of aziridines

Aziridines have been widely implicated in organic synthesis. Due to their strong ring strain, ring-opening reactions of aziridines with many nucleophiles have been reported by numerous groups. In 1976, an access to either syn- or anti- vicinal diamines was developed by Swift and Swern,[129] who disclosed another possibility to synthesize vicinal diamines from aziridines.[130]

A recent study illustrates how this strategy is applied in vicinal diamine synthesis. Gotor and co-workers initially prepared enantiopure aziridines by exploiting the amidase-containing, commercially available bacterium *Rhodococcus rhodochrous* IFO 15564 for the enantioselective hydrolysis of several unactivated 1-benzyl- or 1-arylaziridine-2-carboxamides (Scheme 4.3). [131] The enantiopure aziridines underwent nucleophilic attack by methanol or by sodium azide to afford the enantiopure 1,2-diamines in good yield.



Scheme 4.3 Diamines derived from aziridines

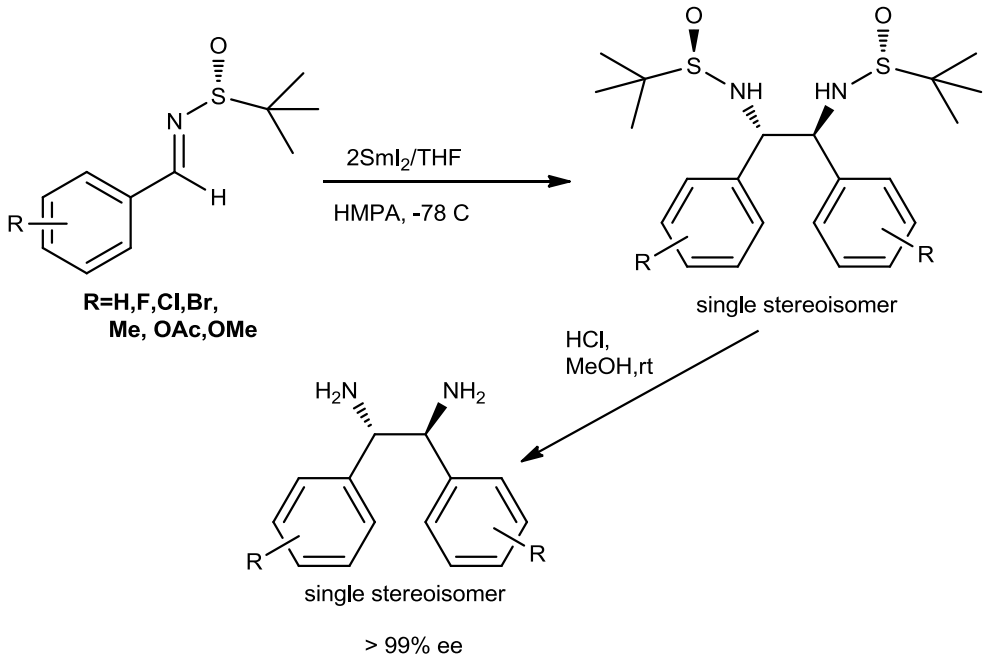
[129] Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511.

[130] (a) Leung, W.-H.; Yu, M.-T.; Wu, M.-C.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 891. (b) Kuroki, T.; Katsuki, T. *Chem. Lett.* **1995**, 337. (c) Dureault, A.; Tranchepain, I.; Greck, C.; Depezay, J.-C. *Tetrahedron Lett.* **1987**, *28*, 3341. (d) Dureault, A. Tranchepain, I. Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 5324. (e) Kelley, B. T.; Joulli é, M. M., *Org Lett.*, **2010,** *12*, 4244.

[131] Moran-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.*, **2007**, *9*, 521.

1.3. Reductive coupling of imines

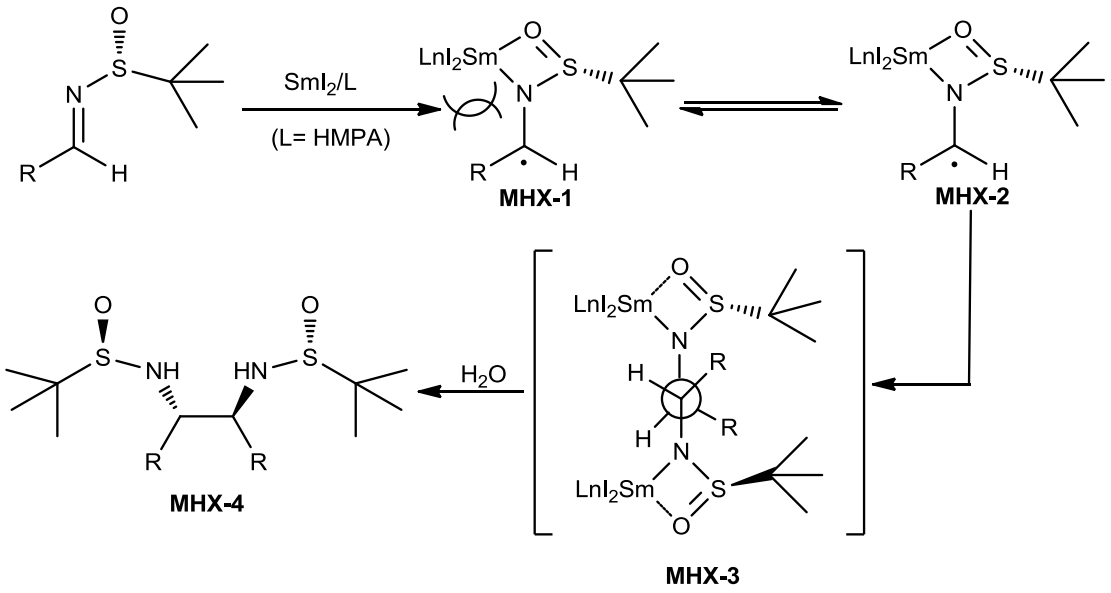
The reductive coupling of imines is one of the most efficient approaches to diamine and has been studied intensively. Recently, Xu and co-workers investigated the reductive coupling of chiral *N*-*tert*-butanesulfinyl imines by exposure to 2 equiv of SmI_2 in the presence of HMPA(Scheme 4.4).[132] The formation of chiral diamines is observed, and this appears to be the first radical dimerization of *N*-*tert*-butanesulfinyl imines that has been reported.



Scheme 4.4 Reductive coupling of imines

A plausible mechanism is shown in Scheme 4.5. The bulkiness of the samarium complex with HMPA results in the rapid formation of the more favorable and stable radical intermediate *trans* **MHX-2** instead of *cis* **MHX-1**. The dimerization of **MHX-2** gives the stable intermediate**MHX-3** which will be converted into the corresponding diamine **MHX-4** by hydrolysis.

[132] (a) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956. (b) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.*, **2004**, *6*, 4747.



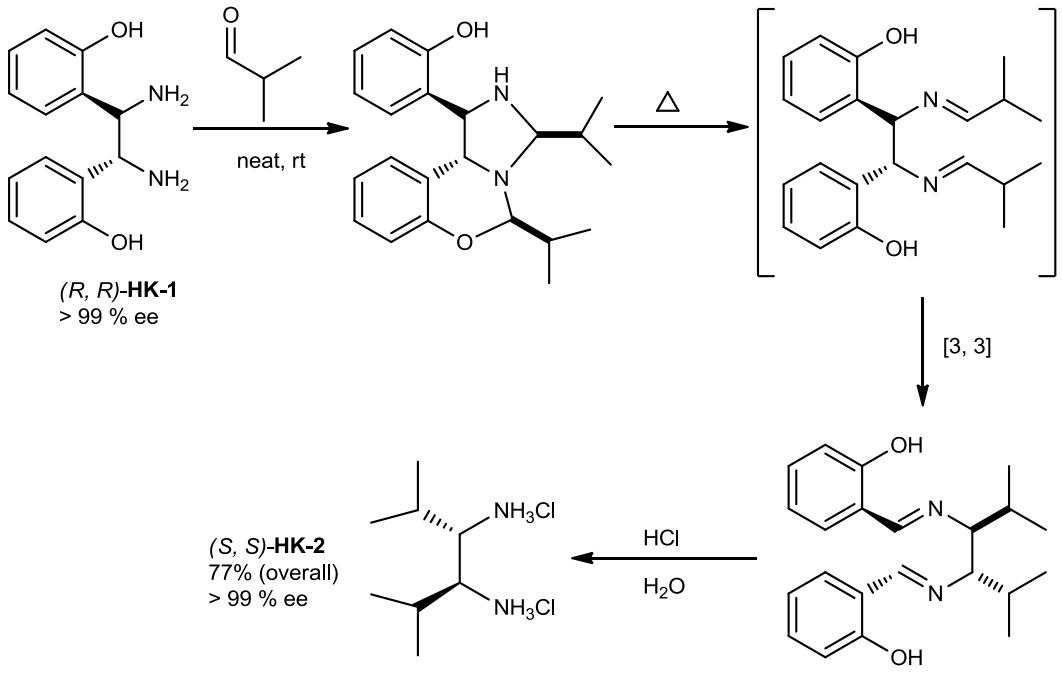
Scheme 4.5 Plausible mechanism

1.4. The Aza-Cope rearrangement

Other powerful methods involving classical named reactions, such as the aza-Cope rearrangement, have been developed by some groups for the construction of diamines. The first synthesis of aryl-substituted meso vicinal diamines via the diaza-cope rearrangement reaction was accomplished by Vogtle and Goldschmitt in 1973.[133] Recently, another strategy was developed by Chin and co-workers. [134] It opens access to the more synthetically challenging alkyl-substituted vicinal diamines via an aza-cope rearrangement. As shown in Scheme 4.6, the "mother diamine" **HK-1** underwent a directed diaza-Cope rearrangement reaction to make enantiopure "daughter" diamines **HK-2**. This is an extremely concise approach to build a chiral diamine library.

[133] Vogtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed.* **1973**, *12*, 767.

[134] (a) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J., *J. Am. Chem. Soc.* **2008**, *130*, 12184. (b) Kim, H.; Staikova, M.; Lough, A. J.; Chin, J. *Org. Lett.*, **2009**, 11, 157.

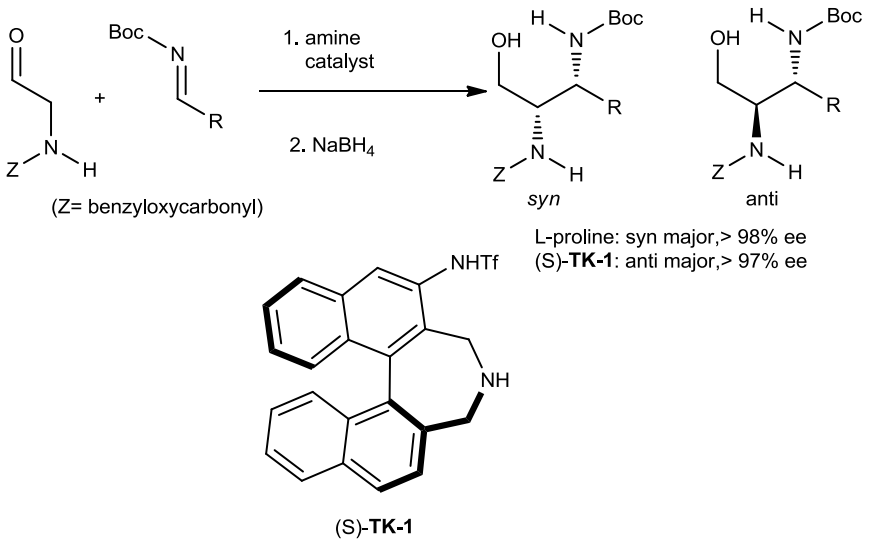


Scheme 4.6 Diaza-Cope rearrangement in diamine synthesis

1.5. The Mannich reaction

The Mannich-Reaction is employed in the organic synthesis of complex compounds bearing amino groups such as peptides, nucleotides, antibiotics, and alkaloids. Therefore, it is not surprising to find that the Mannich reaction has been applied to the synthesis of chiral diamines. Generally, carbonyl compounds having an α-nitrogen functional group can be involved in such kinds of reactions. Recently, a highly stereocontrolled synthesis of vicinal diamines by organocatalytic asymmetric Mannich reaction of *N*-protected aminoacetaldehydes was described by Maruoka and co-workers.[135] As shown in Scheme 4.7, by adding L-proline or the axially chiral amino sulfonamide (S)-**TK-1** as the catalyst, the corresponding *syn* or *anti*- diamines could be readily obtained in high enantiopurity

[135] Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K., *J. Am. Chem. Soc.* **2012,** *134*, 7516.

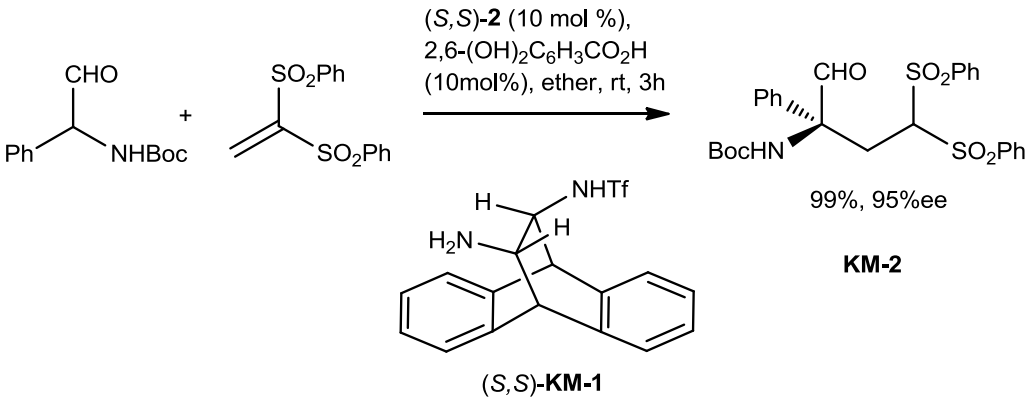


Scheme 4.7 Mannich reaction in diamine synthesis

2. 1,2-Diamines in organic synthesis

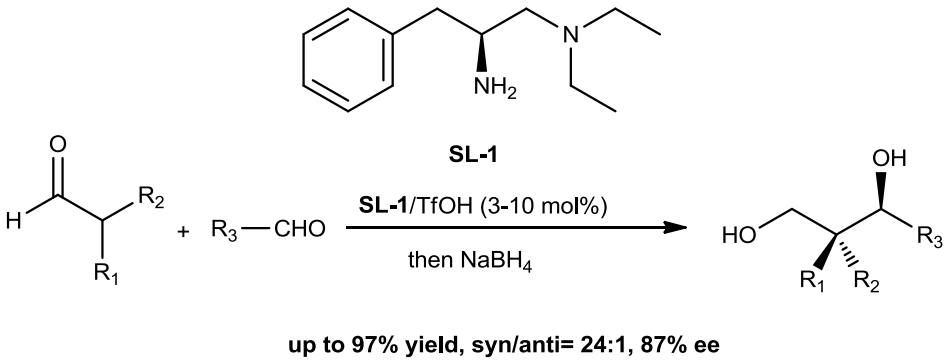
In organic synthesis, vicinal diamines as various chiral ligands play a crucial role especially in the field of catalytic asymmetric synthesis.[136] Therefore, intense efforts have been devoted to their synthesis and applications in organic synthesis. Among recent results, (S,S)-**KM-1** as an asymmetric catalyst used in asymmetric conjugate addition of heterosubstituted aldehydes to vinyl sulfone, was developed by Maruoka and co-workers (Scheme 4.8). It is a highly stereoselective reaction that produces **KM-2** in high yield.[137]

[136] (a) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed.* **1994**, *33*, 497. (b) Tomioka, K. *Synthesis* **1990**, 541.
[137] Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.*, **2010**, *132*, 17074.



Scheme 4.8 Conjugate addition of heterosubstituted aldehydes to vinyl sulfone

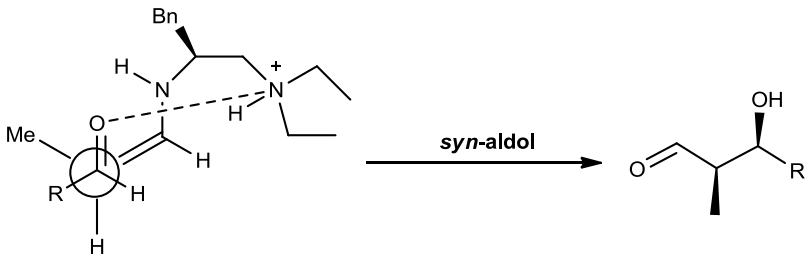
The search for a highly syn-selective cross-aldol reaction of aldehydes has remained a big challenge for chemists.[138] Various vicinal chiral diamines have been screened by Luo and co-workers to mediate syn-selective cross-aldol reactions of aldehydes (Scheme 4.9).[139] L-phenylalanine derived **SL-1**/TfOH was found to be the best catalyst in this cross-aldol reaction of aldehydes. As shown in Scheme 4.10, the corresponding transition state of *syn*-aldol reaction is proposed.



Scheme 4.9 Cross-aldol reaction of aldehydes

[138] (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) List, B. *Chem. Commun.* **2006**, 819. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (e) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2007**, *20*, 131. (f) List, B.; Lerner, R. A.; Barbas, C. F., *J. Am. Chem. Soc.* **2000**, *122*, 2395. (g) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (h) Torri, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (i) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285.

[139] Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010,** *75*, 4501.

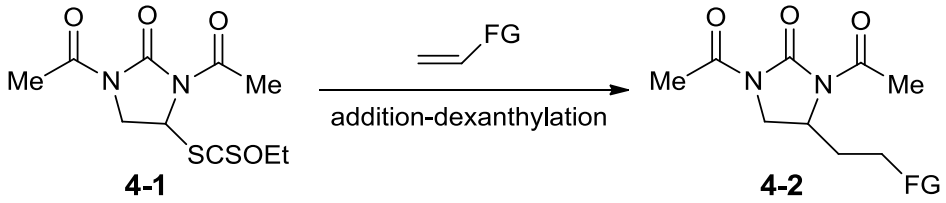


Scheme 4.10

II. Synthesis of 1,2-diamine via degenerative transfer of xanthates onto alkenes

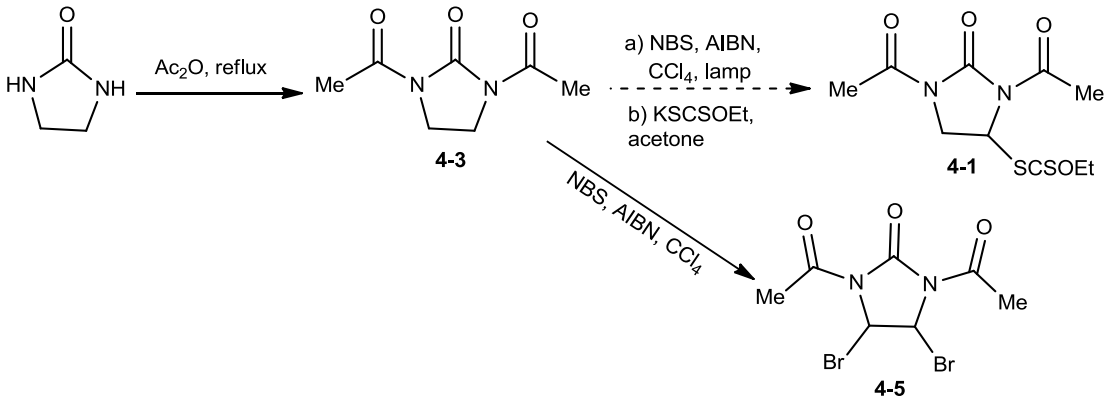
1. Radical addition of xanthates to 1,2-diaminoalkenes

The radical addition of xanthates to alkenes allows a modular, convergent access to complex structures. For the synthesis of 1,2-diamines, we considered the utilisation of xanthate **4-1** and as a flexible reagent for the preparation of 1,2-diamines as pictured in Scheme 4.11.



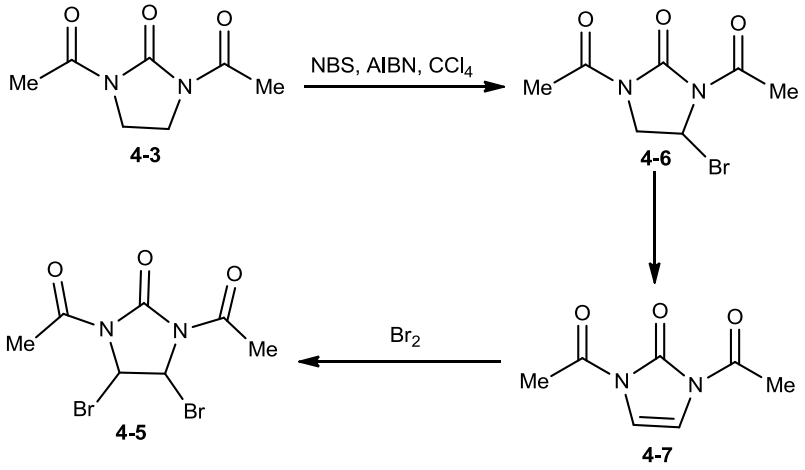
Scheme 4.11

First we tried the bromination of **4-3** using the Wohl-Ziegler reaction as a potentially rapid route to xanthate **4-1**. Since imidazolidin-2-one is quite cheap and readily available, its acylation could furnish **4-3** as the starting material for the bromination reaction. However, as illustrated in Scheme 4.12, using the same bromination procedure, a mixture of dibrominated and unsaturated products **4-5** and **4-7** were observed instead of the desired mono brominated product.



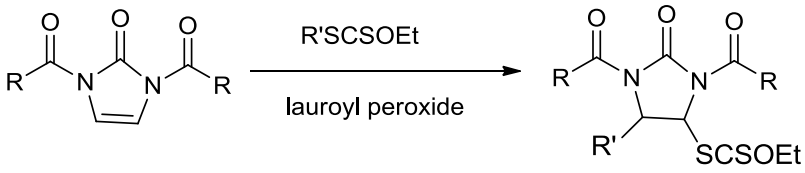
Scheme 4.12 Synthesis of xanthate **4-1**

The dibrominated product could arise from the bromination of **4-7** generated from the elimination of **4-6** (Scheme 4.13). A possible remedy was to lower the concentration of the bromine by diluting the solution and adding the NBS portion-wise over a longer period. Unfortunately, even under quite dilute conditions, none of the desired mono brominated product **4-6** was observed in the crude NMR spectrum.



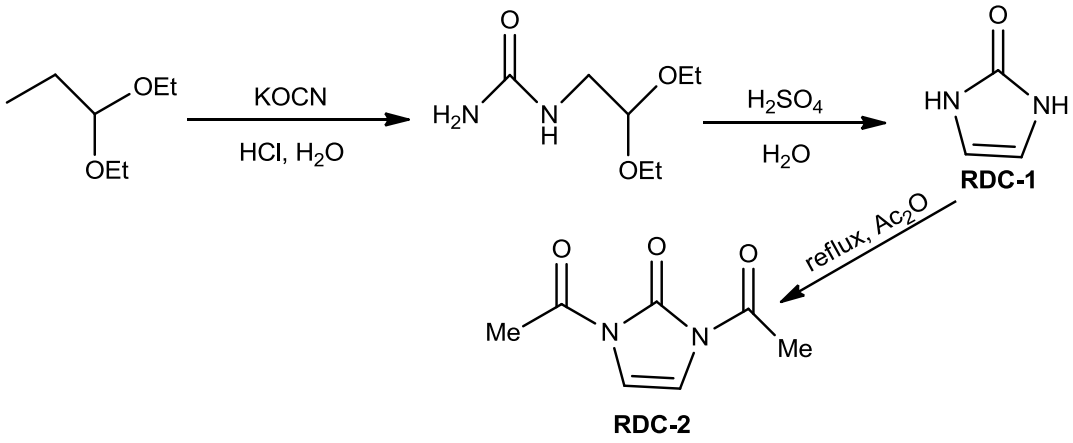
Scheme 4.13 Bromiantion of **4-3**

The unsuccessful bromination of **4-3** persuaded us to find an alternative method for the synthesis of xanthate **4-1**. In 2010, Guillaume Revol reported a powerful strategy for the preparation of complex primary amines based on the radical addition of various xanthates to *N*-vinyl phthalimide. Therefore, we next tested the applicability of this method for the synthesis of 1,2-diamines as shown in Scheme 4.14.



Scheme 4.14

Following the literature procedure, alkene **RDC-1** was quickly available via two steps on multigram scale.[140] The formation of ureidoacetaldehyde diethyl acetal was accomplished by treatment of aminoacetaldehyde diethyl acetal with potassium cyanate in aqueous HCl. In the presence of sulfuric acid, this white crystalline solid undergoes a dehydrative intramolecular cyclization to form 2-imidazolinone **RDC-1** in good yield. With quantities of 2-imidazolinone **RDC-1** in hand, we prepared 1,3-diacetyl-1,3-dihydro-2*H*-imidazol-2-one **RDC-2** by the same acetylation procedure as for imidazolidin-2-one **4-3**.

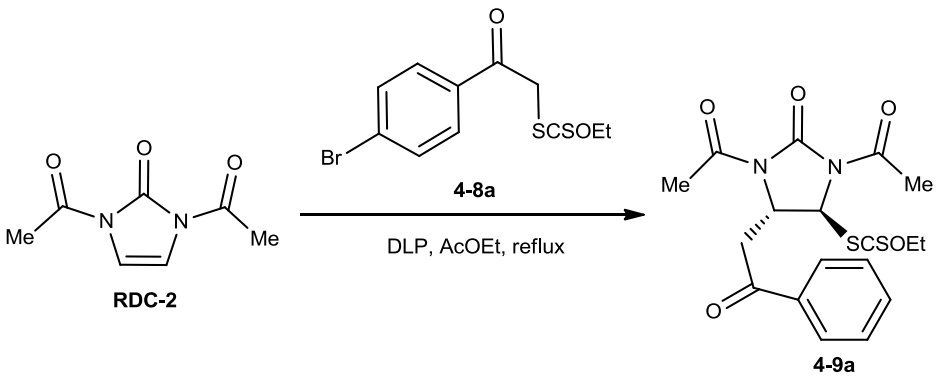


Scheme 4.15 Synthesis of **RDC-2**

We first tried the radical addition of xanthate **4-8a** to olefin **RDC-2** according to the general procedure and added excess olefin **RDC-2**. However, a large amount of oligomer was then observed. Probably, as for *N*-vinyl phthalimide, olefin **RDC-2** is an active alkene which generates a stable radical to form the oligomer during this radical

[140] Fischer, W.; Hollins, R. A.; Lowe-Ma, C. K.; Nissan, R. A.; Chapman, R. D. *J. Org. Chem.* **1996**, *61*, 9340.

process. Therefore, applying the same approach as for the radical addition of xanthates to *N*-vinyl phthalimide, we lowered the concentration of the solution and increased the ratio of xanthate **4-8a** to olefin **RDC-2**, in order to reduce the chances to form oligomer. After a simple optimization, the yield of adduct **4-9a** increased to 62% (Scheme 4.16).



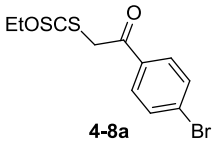
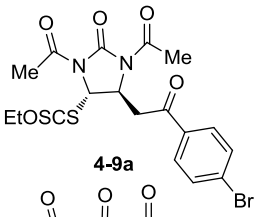
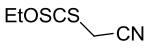
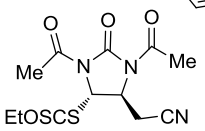
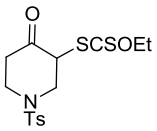
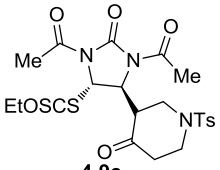
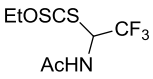
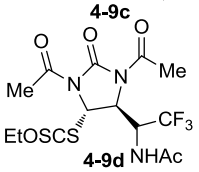
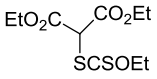
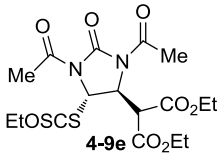
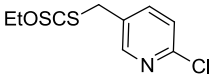
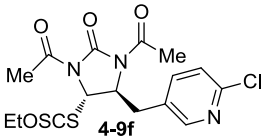
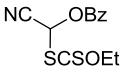
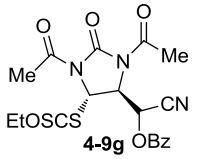
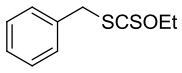
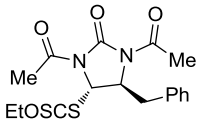
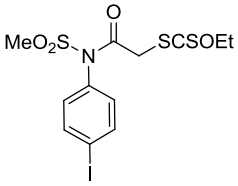
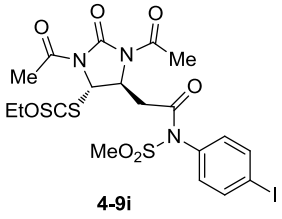
Concentration	Xanthate **4-8a**	Yield %
1 M	1.5 equiv.	trace
0.5 M	2 equiv.	33%
0.25 M	3 equiv.	62%

Scheme 4.16 Synthesis of **4-9a**

As shown by the results in Table 1, the radical addition of various xanthates **4-8** to **RDC-2** gave generally good yields of the *trans* adduct **4-9**. It is worthwhile to note that the radical addition of xanthates **4-8** to alkene **RDC-2** gives only *trans* adducts **4-9** in a highly stereoselective process. Addition of the carbon radical from the xanthate onto one face of alkene **RDC-2** leads an intermediate radical where this face is now sterically blocked, forcing the transfer of the xanthate from the opposite side.

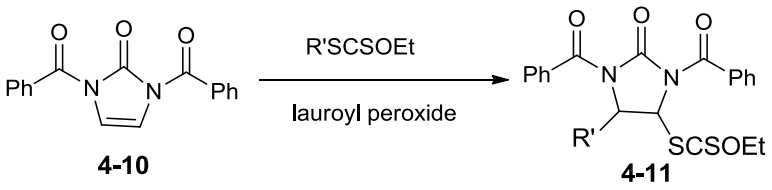
Furthermore, it is clear from the transformations in Table 4.1 that numerous functional groups may be introduced through the xanthate partner **4-8**. Therefore, functionality in the xanthate allows the incorporation of an aryl, a cyano, a protected cyclic or open-chain amino, a trifluoromethylamino, or a heterocyclic groups. The presence of the xanthate group in the adducts should allow for a second radical addition.

Table 4.1 Diamine **4-9**

Xanthate **4-8**	Radical adduct **4-9**	Yield %	DLP %	
 **4-8a**	 **4-9a**	62%	45%	
 **4-8b**	 **4-9b**	76%	10%	
 **4-8c**	 **4-9c**	61%	55%	dr:3:2[a]
 **4-8d**	 **4-9d**	68%	45%	dr:2:1[a]
 **4-8e**	 **4-9e**	88%	15%	
 **4-8f**	 **4-9f**	54%	60%	
 **4-8g**	 **4-9g**	68%	45%	dr:1:1[a]
 **4-8h**	 **4-9h**	56%	45%	
 **4-8i**	 **4-9i**	52%	30%	

[a] The dr was measured by NMR spectroscopy after purifiction by column chromatography.

In order to fine tune the stability of the alkene and perhaps improve the efficiency, we replaced the acetyl by benzoyl as the *N*-protecting group and then alkene **4-10** was prepared by standard benzoylation. The radical addition of several xanthates to alkene **4-10** was then investigated.

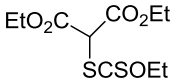
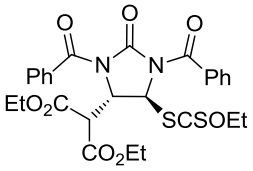
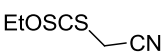
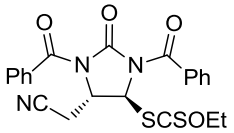
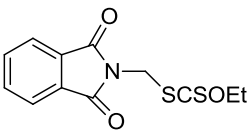
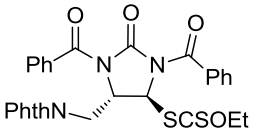


4-10 **4-11**

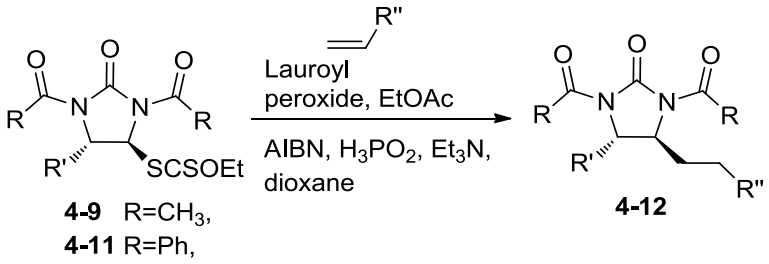
Scheme 4.17 Synthesis of **4-11**

The radical addition required in general a little bit more DLP as compared with alkene **RDC-2** (Scheme 4.17). The benzoyl group may stabilize the carbon radical somewhat better than acetyl group, but this does not make a significant difference in the efficiency. Not surprisingly, the *trans* adducts **4-11** were the only products as indicated in Table 4.2.

Table 4.2 Diamine **4-11**

Xanthate **4-8**	Radical adduct **4-11**	Yield %	DLP %
 **4-8e**	 **4-11a**	92%	15%
 **4-8b**	 **4-11b**	85%	20%
 **4-8h**	 **4-11c**	62%	45%

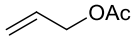
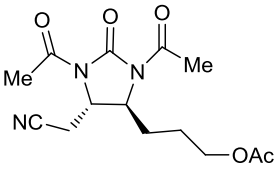
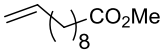
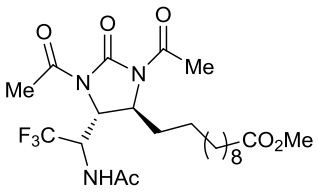
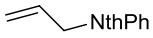
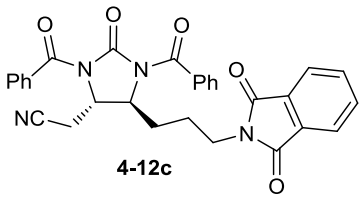
After we gained some experience in synthesis of these adducts, we examined the radical additions of those adducts **4-9** or **4-11** to various unactivated olefins (Scheme 4.18). We were quite delighted to observe the formation of the corresponding adduct **4-12** after a short reaction time. Reductive removal of the xanthate group simplified their NMR spectra and their characterization. Furthermore, the C-C bond formation, as expected, takes place from the opposite side to the R' side chain with net overall retention of configuration.



Scheme 4.18 Secondary radical addition

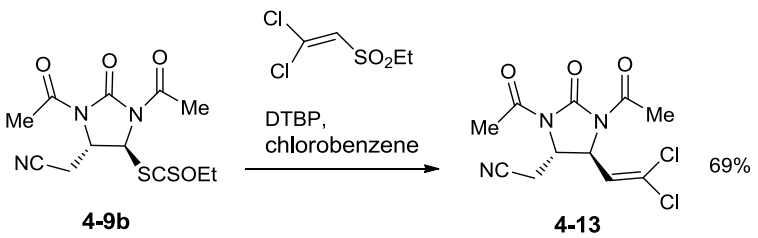
As shown in Table 4.3, the more complex *trans* diamines **4-12** can thereby be obtained in good yield for the combined two steps, which demonstrates the efficient radical additions of these newly synthesized diamine xanthates to various unactivated olefins. Furthermore, the radical addition of adduct **4-9d,** which is a triamine bearing a trifluoromethyl group, to various olefins can be considered as a concise and diverse synthetic route to access such kinds of triamines which would be extremely difficult to obtain by more conventional approaches. The addition of adduct **4-11b** to *N*-allyl phthalimide introduces another protected amino unit to the final diamine product, and this is another interesting triamine structure.

Table 4.3 Diamine **4-12**

Xanthate	Alkene	Radical adduct **4-12**	Yield % step1+step2	step1 DLP %
4-9b		 **4-12a**	54%	25%
4-9d		 **4-12b**	68%	10%
4-11b		 **4-12c**	64%	10%

2. Extension of 1,2-diamine synthesis

To extend the scope of this strategy, we carried out the transformation pictured in Scheme 4.19. As discussed in the introduction, the addition of xanthate **4-9b** to 1,1-dichloro-2-(ethylsulfonyl)ethylene gave diamine **4-13** in good yield. The dichlorovinyl motif may be converted into an alkyne by the powerful Corey-Fuchs reaction or used in organometallic coupling reactions.[141]

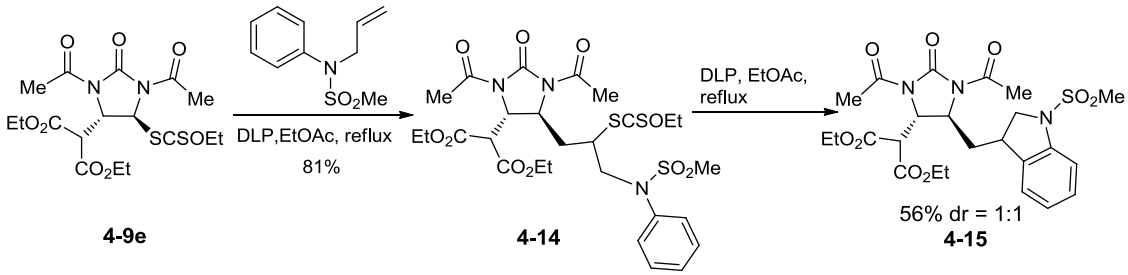


4-9b **4-13**

Scheme 4.19

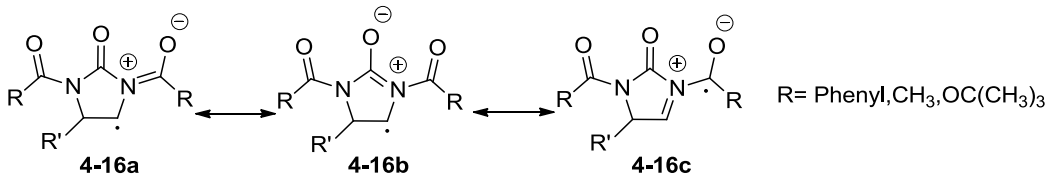
[141] Li, Z.; Zard, S. Z., *Org. Lett.* **2009**, *11*, 2868.

Another equally interesting extension is the combination of the diamine unit with an indoline. As illustrated in Scheme 4.20, we successfully incorporated the protected diamine unit to indoline **4-15** via a sequential radical addition and cyclization process. Based on this interesting structure **4-15**, the synthesis of more complex polycyclic compounds could be envisaged.



Scheme 4.20

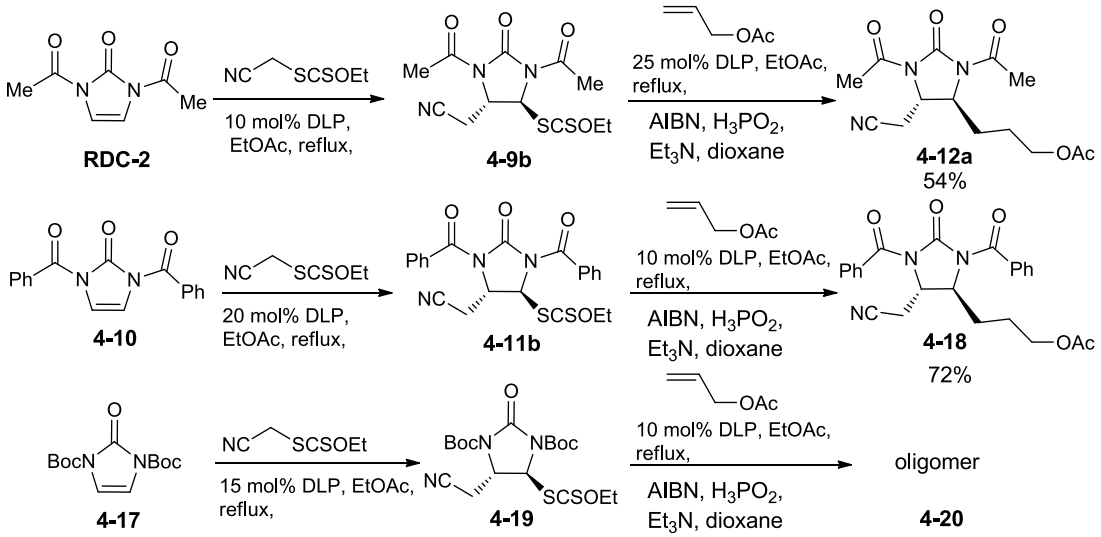
The success of the second addition can be explained by canonical forms **4-16 a-d** as shown in Scheme 4.21, which suggests how this imide structure could stabilize the radical intermediate. By replacing the acetyl with a benzoyl, we found, in general, that the first addition to the benzoyl protected olefin **4-10** with the same xanthate required more DLP to complete the reaction a compared with the acetyl analog. In the second radical additions to allyl acetate, a small amount of oligomer (double and triple addition to allyl acetate) could be observed in the case of the xanthate derived from olefin **RDC-2** and consequently, the second addition is more efficient in the benzoyl protected series.



Scheme 4.21 Canonical forms **4-16 a-c**

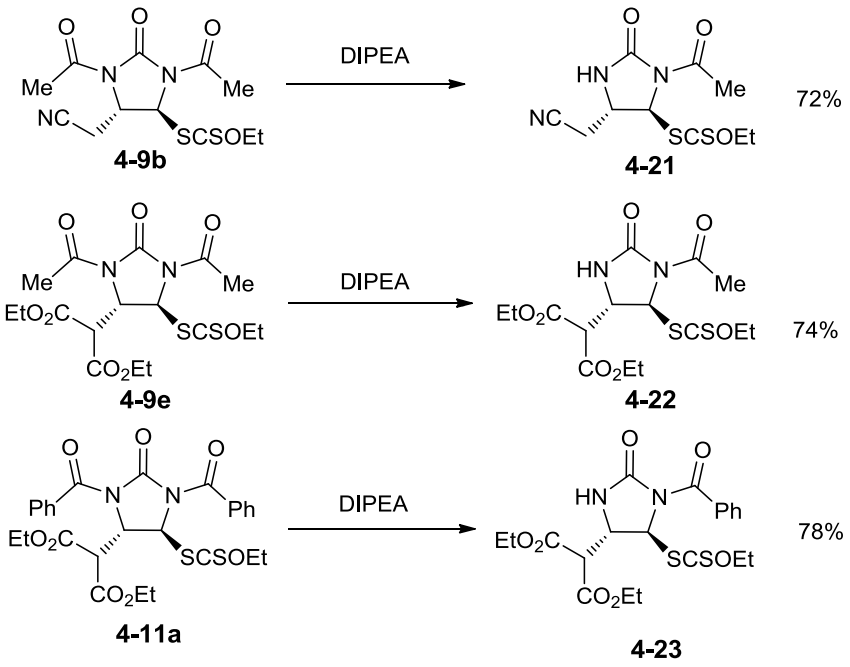
To better understand the stability of radical intermediates bearing different protecting groups, we started an investigation using acetyl, benzoyl or Boc as the

nitrogen protecting group. The sequential two radical additions involve the same xanthate and ally acetate as the second olefin. The results shown in Scheme 4.22 seem to suggest the notion that the greater resonance stabilization is provided by the benzoyl substituent in **4-11b** than by the acetyl substituent in **4-9a**.



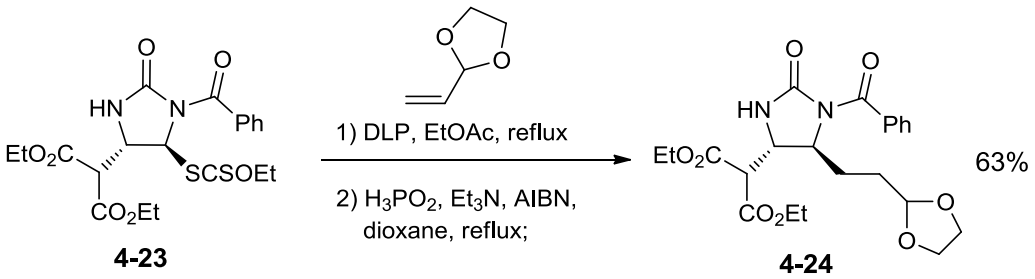
Scheme 4.22

An interesting observation concerning the protecting group is that the acyl group on the nitrogen distal from the xanthate can be selectively removed by *N*,*N*-diisopropylethylamine in high yield (Scheme 4.23). The causes underlying this regioselectivity are not clear. It is obviously not steric since both nitrogens appear to be comparably hindered



Scheme 4.23 Selective deprotection

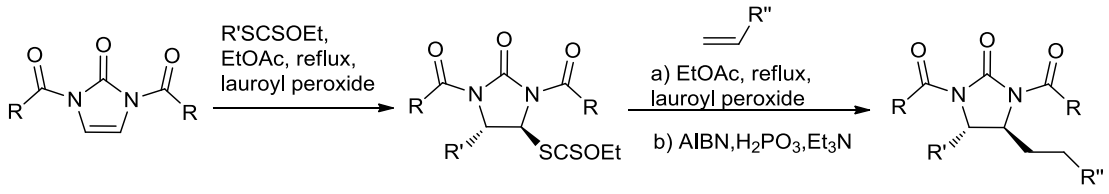
The mono protected diamine xanthate **4-23** was able to undergo a second radical addition. As shown in Scheme 4.24, the radical addition and reductive removal of the xanthate group furnished the corresponding protected diamine **4-24**. In the product the two nitrogens are clearly differentiated allowing subsequent regioselective modification.



Scheme 4.24

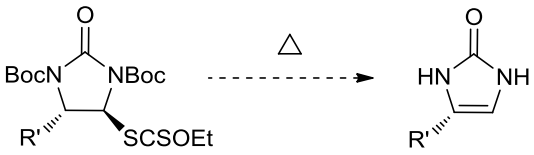
Conclusion

As summarized in Scheme 4.25, a modular and concise approach to access highly functionalized 1,2-diamines was investigated by us. The examples displayed in Table 4.1, Table 4.2 and Table 4.3 demonstrate that the radical addition of xanthates to 1,2-diamino substituted olefins followed by a second addition represents a highly efficient route to produce diversely complex 1,2-diamine structures. This approach complements the previous ones developed earlier. Taken together, these various transformations constitute a significant contribution to the synthesis of amines.



Scheme 4.25

Ongoing work to further explore the scope of this method is in progress. One reaction being tested is the possible elimination of the xanthate group by thermolysis of the addition products (Scheme. 4.26).



Scheme 4.26

Chapter 5

Radical Synthesis of Highly Substituted Boc-Protected 4-Aminomethyl-Pyrroles

Introduction

Pyrroles represent indispensable structural motifs of biologically active alkaloids, pharmaceutical products, or even materials such as conducting polymers.[142] For instance, lipitor, a pyrrole based hypochloremic agent, was for many years the largest selling drug, with annual sales in excess of 10 billion U.S. Dollars.[143] 2,4-Disubstituted pyrroles are especially interesting since they are useful intermediates for the synthesis of more highly substituted derivatives and are present in a few pharmacologically significant products.[144] Three examples of 2,4-disubstituted pyrrole natural products are displayed in Figure 5.1: Hymenidin is an antagonist of serotonergic receptors; pyrrolostatin is a potent inhibitor of lipid peroxidation, and heronapyrroles A and B display antibiotic activity against Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis.

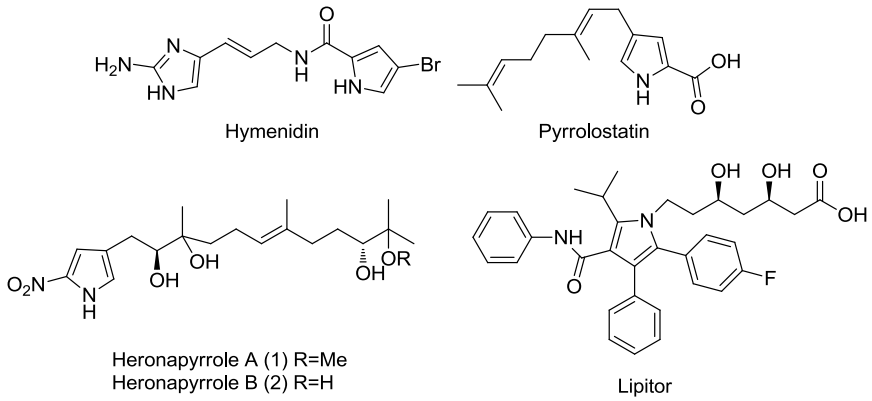


Figure 5.1 Structures of biologically active pyrroles

[142] (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.; *Chem. Rev.*, 2008, **108**, 264. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.*, 2006, **23**, 517. (c) Gale, P. A. *Acc. Chem. Res.* 2006, **39**, 465. (d) Baraldi, P. G.; Nunez, M. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Esterez, F.; Romagnodi, R. *J. Med. Chem.*, 2004, **47**, 2877. (e) Srivastava, S. K.; Shefali Miller, C. N.; Aceto, M. D.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M.; *J. Med. Chem.*, 2004, **47**, 6645.

[143] Thompson, R. B. *FASEB J.* **2001**, *15*, 1671.

[144] (a) Bergauer, M.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1937. (b) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176. (c) Han, S.; Siegel, D. S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2013**, *78*, 11970. (d) Kato, S.; Shindo, K.; Kawai, H.; Odagawa, A.; Matsuoka, M.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 892. (e) Raju, R.; Piggott, A. M.; Barrientos Diaz, L. X.; Khalil, Z.; Capon, R. J. *Org. Lett.* **2010**, *12*, 5158.

There are numerous synthetic methods for the construction of pyrrole structures. In this chapter, therefore the classic named reactions and current methods for the preparation of pyrroles will be briefly discussed. However, the limitations of most known approaches to access 2,4-disubstituted and polysubstituted pyrroles bearing a protected aminomethyl group encouraged us to apply our typical radical addition process for the construction of such pyrroles. Thus, the scope and advantages of our newly designed protocol for the preparation of 2-disubstituted, 2,3-trisubstituted and polycyclic, boc-protected 4-aminomethyl-pyrroles will also be then described in this chapter.

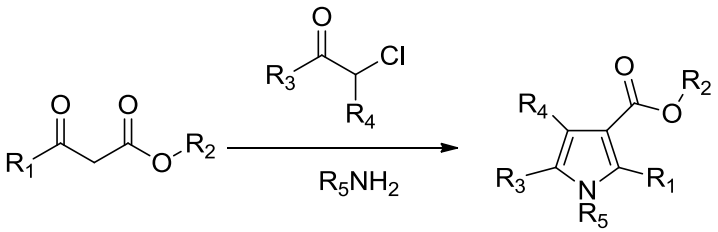
Ⅰ. Synthesis of pyrroles

1. Named reactions for pyrrole synthesis

There is a plethora of methods to access pyrroles, especially the classical named reaction such as the Hantzsch synthesis, Paal–Knorr synthesis or Barton-Zard reaction which open up numerous opportunities for the synthesis of pyrroles.

1.1. The Hantzsch Pyrrole Synthesis

In 1890, Hantzsch reported the preparation of pyrroles via the condensation of *α*-halo-ketones, *β*-ketoesters and ammonia or amines, which is generally referred to as the Hantzsch pyrrole synthesis or Hantzsch synthesis (Scheme 5.1).[145]

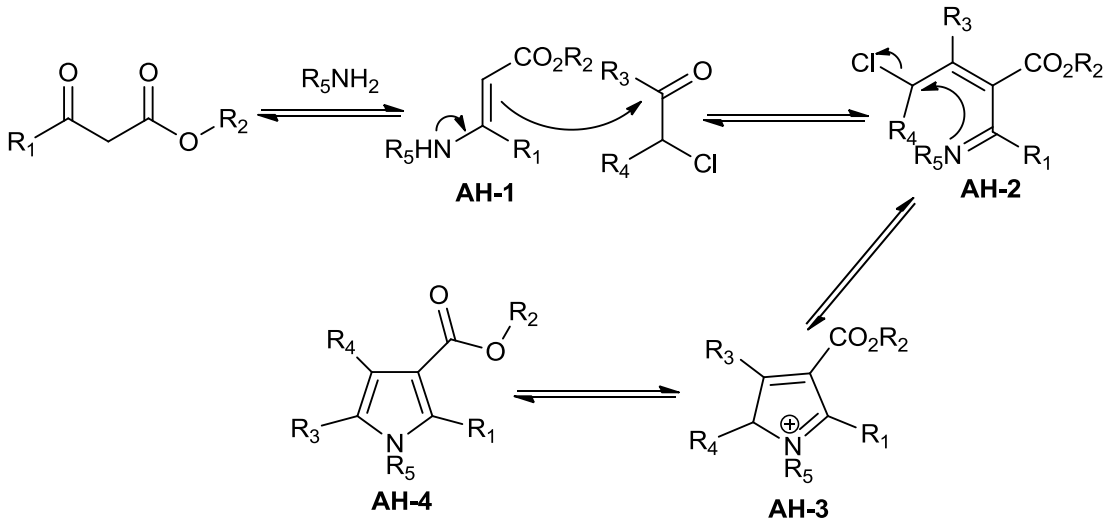


Scheme 5.1 Hantzsch pyrrole synthesis

The mechanism is outlined in Scheme 5.2. Condensation of ammonia or primary amine with *β*-ketoesters gives enamine **AH-1,** which then attacks the carbonyl carbon of the *α*-haloketone to furnish intermediate **AH-2**. This is quickly converted to 5-membered ring **AH-3** *via* an intramolecular nucleophilic attack. Finally, the aromatization of **AH-3** affords the corresponding pyrrole **AH-4**. Since this reaction consists of three components, a wide scope of functional groups could in principle be incorporated by replacing the substituents on the different components to give

[145] (a) Hantzsch, A. *Ber*. **1890**, *23*, 1474. (b) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron* **1987**, *43*, 5171. (c) Kirschke, K.; Costisella, B.; Ramm, M.; Schulz, B. *J. Prakt. Chem*. **1990**, *332*, 143. (d) Kameswaran, V.; Jiang, B. *Synthesis* **1997**, 530.

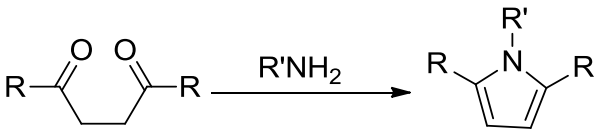
numerous pyrrole derivatives.[146] The Hantzsch synthesis can be considered as the most appropriate approach for accessing highly substituted pyrroles. Furthermore, this reaction has been extended to the preparation of indoles and carbazoles.



Scheme 5.2 Mechanism of the Hantzsch pyrrole synthesis

1.2. The Paal–Knorr pyrrole synthesis

Knorr initially described this synthesis in 1884 and later the condensation between 1,4-dicarbonyls and primary amines (or ammonia) giving pyrroles was defined as the Paal-Knorr Pyrrole Synthesis (Scheme 5.3).[147]

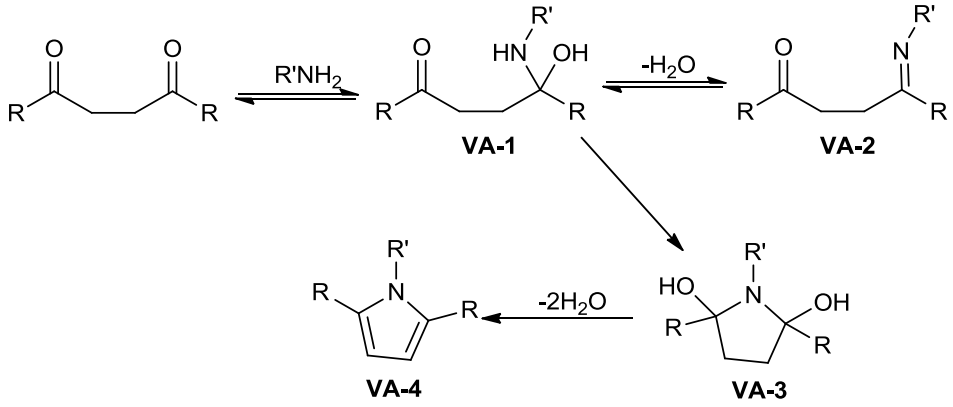


Scheme 5.3 The Paal–Knorr pyrrole synthesis

[146] (a) Trautwein, A. W.; Süβmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. (b) Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

[147] (a) Paal, C. *Ber.* **1885**, *18*, 367. (b) Chiu, P. K.; Sammes, M. P. *Tetrahedron* **1988**, *44*, 3531. (c) Gribble, G. W. *Knorr and Paal–Knorr Pyrrole Syntheses*. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Corey, E. J., Eds, Wiley: Hoboken, NJ, **2005**, 77.

Amarnath and co-workers investigated the mechanism of this process (Scheme 5.4).[148] Their work suggested that hemiaminal **VA-1** is a crucial intermediate that is formed by the nucleophilic attack of the amine on the ketone under acidic conditions. The hemiaminal **VA-1** then undergoes an intramolecular nucleophilic attack to afford intermediate **VA-3** followed by the dehydration to furnish the corresponding pyrrole **VA-4**. All 1,4-dicarbonyls, *α*-amino ketones or *α*-amino-*β*-ketoesters can be converted into the corresponding pyrroles by modification of this method. The reaction requires mild acidic conditions and tolerates a wide range of functional groups. These advantages make the Paal–Knorr a powerful tool for pyrrole synthesis.[149]



Scheme 5.4 Mechanism of the Paal–Knorr pyrrole synthesis

1.3. The Barton-Zard reaction

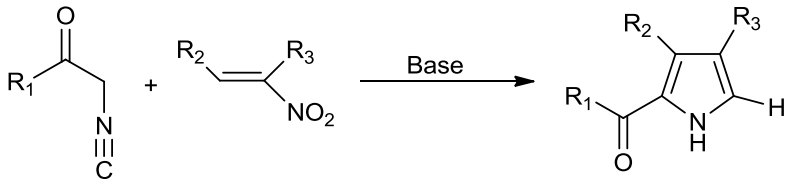
In 1986, Barton and Zard reported the formation of pyrroles *via* condensation of a substituted nitro-alkene with an isocyanoester in the presence of base. This is now called the Barton-Zard pyrrole synthesis (Scheme 5.5).[150] It is particularly adapted for the synthesis of pyrroles with various substituents at the 3,4 positions (R_2 and R_3) and the 2 position can be temporally blocked by a *t*-butyl carboxylate, a group that is

[148] Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924.

[149] (a) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443. (b) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 7352.

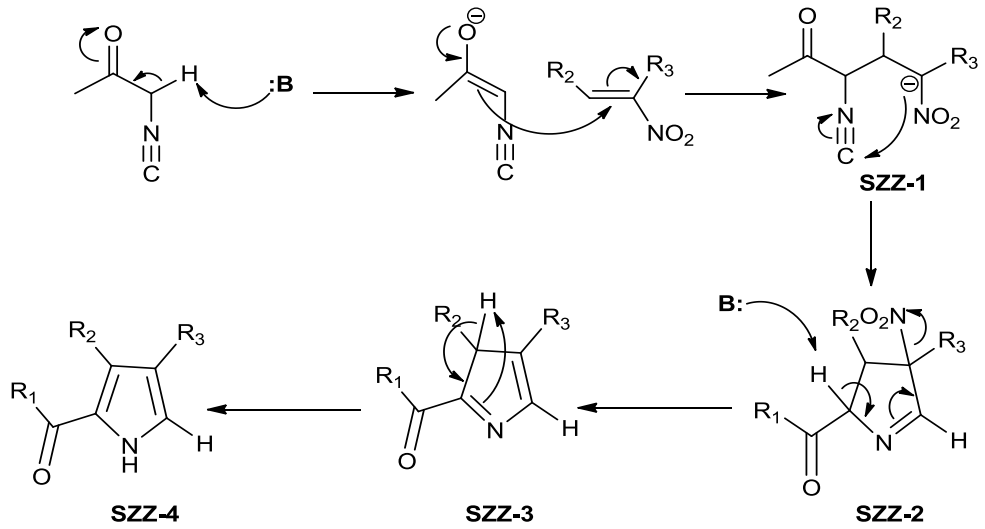
[150] (a) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.

difficult to introduce by other procedures.[151] The preparation of functional dyes, polypyrroles, and porphyrins fused with various aromatic rings or bicyclic frameworks have been achieved *via* this approach.[152]



Scheme 5.5 The Barton-Zard reaction

The mechanism is shown in Scheme 5.6. In the presence of base the deprotonated *α*-isocyanide undergoes Michael addition with the nitroalkene to form adduct **SZZ-1**. This is then converted into 5-member ring intermediate **SZZ-2** *via* an intramolecular nucleophilic attack. Finally, the base catalyzed elimination of a nitrite transforms **SZZ-2** into **SZZ-3** followed by aromatization to the corresponding pyrrole **SZZ-4**.



Scheme 5.6 Mechanism of the Barton-Zard reaction

[151] (a) Pelkey, E. T.; Chang, L.; Gribble, G. W. *Chem. Commun.* **1996**, 1909. (b) Ono, N.; Hironaga, H.; Ono, K.; Kaneko, S.; Murashima, T.; Ueda, T.; Tsukamura, C.; Ogawa, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 417.

[152] Lash, T. D.; Werner, T. M.; Thompson, M. L.; Manley, J. M. *J. Org. Chem.* **2001**, *66*, 3152.

2. Recent approaches to construct highly substituted pyrrole derivatives

The need for highly flexible and efficient syntheses of polysubstituted pyrroles has encouraged extensive studies to achieve this goal.[153] Therefore, besides classical named reactions, there has been a plethora of more recent methods for the synthesis of pyrroles, most of which are metal-based or 1,3-dipolar cycloaddition strategies.[154] In the following part, three illustrations of recent approaches to afford highly substituted pyrrole derivatives will be briefly discussed.

2.1. The Hantzsch pyrrole synthesis by using high-speed vibration milling technique

Recently, Menendez and co-workers reported a flexible one-pot process to access highly substituted pyrroles under solvent-free conditions.[155] As shown in Scheme 5.7, the system consisted of ketone **JCM-1**, a primary amine and a *β*-dicarbonyl compound. First, the mixture of ketone **JCM-1** and *N*-iodosuccinimide was heated in the presence of *p*-toluenesulfinic acid to generate intermediate **JCM-2** followed by addition of the primary amine, the *β*-dicarbonyl compound, and 5% cerium (IV) ammonium nitrate (CAN) as the catalyst and silver nitrate (1.0 eq. with

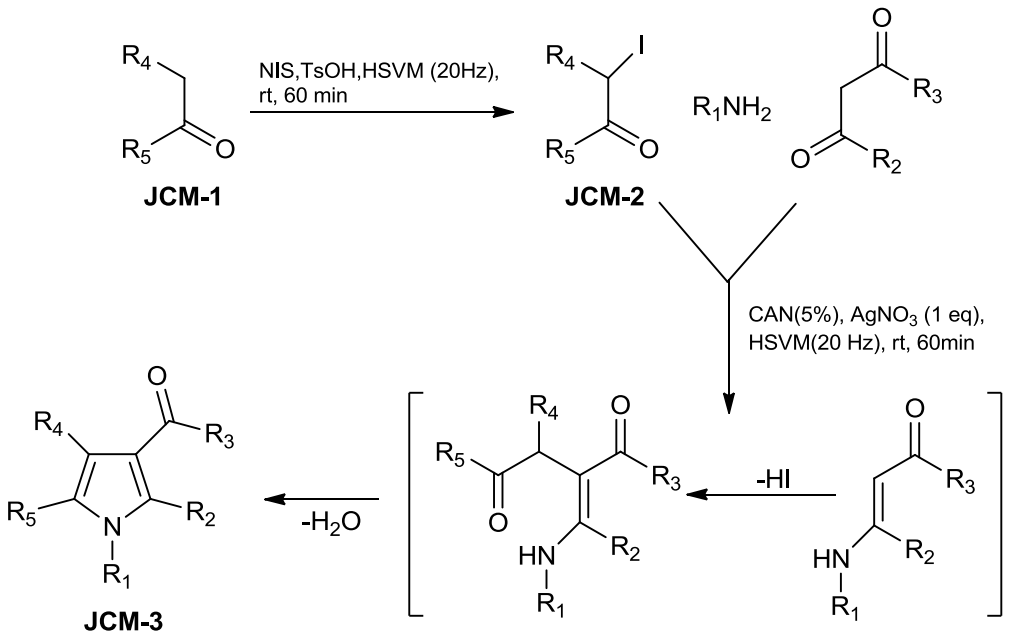
---

[153] (a) *Pyrroles, Part II;* Jones, R. A., Ed.; Wiley: New York, 1992. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, p 119ff.

[154] (a) Yan, R.; Kang, X.; Zhou, X.; Li, X.; Liu, X.; Xiang, L.; Li, Y.; Huang, G. *J. Org. Chem.* **2014**, *79*, 465. (b) Yeh, M.-C. P.; Lin, M.-N.; Hsu, C.-H.; Liang, C. J. *J. Org. Chem.* **2013**, *78*, 12381. (c) Zhou, Y.; Yan, X.; Chen, C.; Xi, C. *Organometallics* **2013**, *32*, 6182. (d) Shi, Y.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 5394. (e) Chaudhuri, R.; Uli Kazmaier, U. *Organometallics* **2013**, *32*, 5546. (f) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (g) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712. (h) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246. (i) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298. (j) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146. (k) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. *Org. Lett.* **2013**, *15*, 2542. (l) Gabriele, B.; Veltri, L.; Plastina, P.; Mancuso, R.; Vetere, M. V.; Maltese, V. *J. Org. Chem.* **2013**, *78*, 4919. (m) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (n) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716.

[155] Estevez, V.; Villacampa, M.; Menendez, J.C. *Chem. Commun.* **2013**, *49*, 59

respect to **JCM-1**) used to trap HI. Under these conditions, the desired pyrrole **JCM-3** could be formed after an additional one hour.

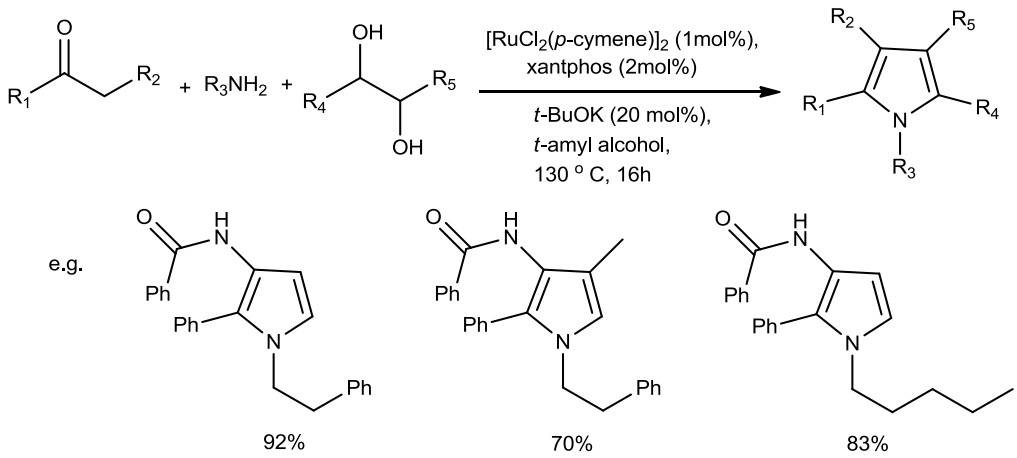


Scheme 5.7 Synthesis of pyrrole under solvent-free conditions

2.2. Pyrrole synthesis based on a ruthenium catalyzed reaction

A general and highly regioselective synthesis of pyrroles based on ruthenium catalysis was described by Beller and co-workers.[156] As shown in Scheme 5.8, in one pot process, various ketones, amines and vicinal diols were converted into the corresponding pyrrole in the presence of the commercially available ruthenium catalyst and a catalytic amount of base. All kinds of substituted pyrroles can be obtained by replacing the R groups in each component. In some cases, even an amide group could be attached to the pyrrole nucleus directly by this method.

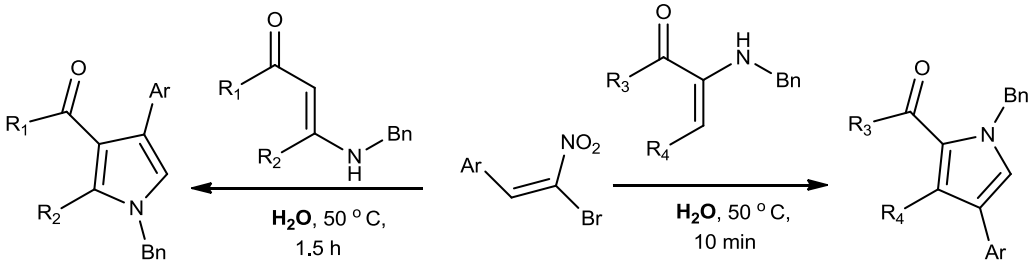
[156] Zhang, M., Fang, X., Neumann, H., Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384.



Scheme 5.8 Ruthenium catalyzed pyrrole synthesis

2.3. Synthesis of pyrroles by domino reaction in water

Most of the known methods for the synthesis of pyrroles require either harsh conditions or are based on metal catalyzed approaches. Recently, Rueping and co-workers applied a domino reaction for the synthesis of pyrroles.[157] As described in Scheme 5.9, and without involving in any metal catalyst, the reaction between (E)-*β*-bromonitrostyrenes and enaminones proceeded in water to furnish 2,3,4-trisubstituted pyrroles under mild conditions. The use of water offers environmental and industrial benefits.



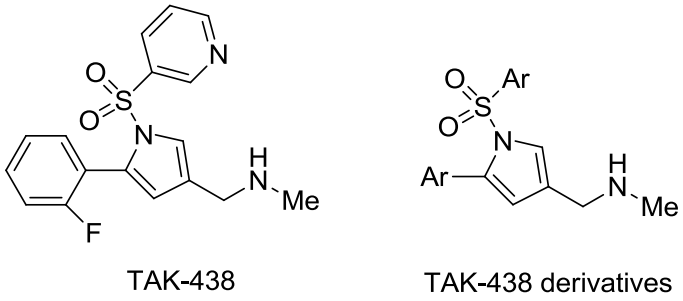
Scheme 5.9 Synthesis of pyrrole in water

[157] Rueping, M., Rarra, A. *Org. Lett.* **2010**, *12*, 5281

Π. Synthesis of TAK-438 and related aminomethyl substituted pyrroles

1. Synthesis of TAK-438

TAK-438 is an unusual pyrrole bearing a strong basic moiety that was discovered by Takeda (Scheme 5.10).[158] The Takeda chemists investigated the synthesis and structure-activity relationships of TAK-438 and its derivatives, which belonged to a new class of inhibitors called potassium-competitive acid blockers (P-CABs).[159] It has been found that the introduction of an aminomethyl group at the 4-position of the pyrrole ring improved its potential greatly as an unprecedented gastric antisecretory agent for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer and other gastric acid-related diseases.[160] Recently, the Takeda Pharmaceutical Company Limited ("Takeda") has submitted a New Drug Application to the Ministry of Health, Labour and Welfare for TAK-438 (generic name: Vonoprazan Fumarate).



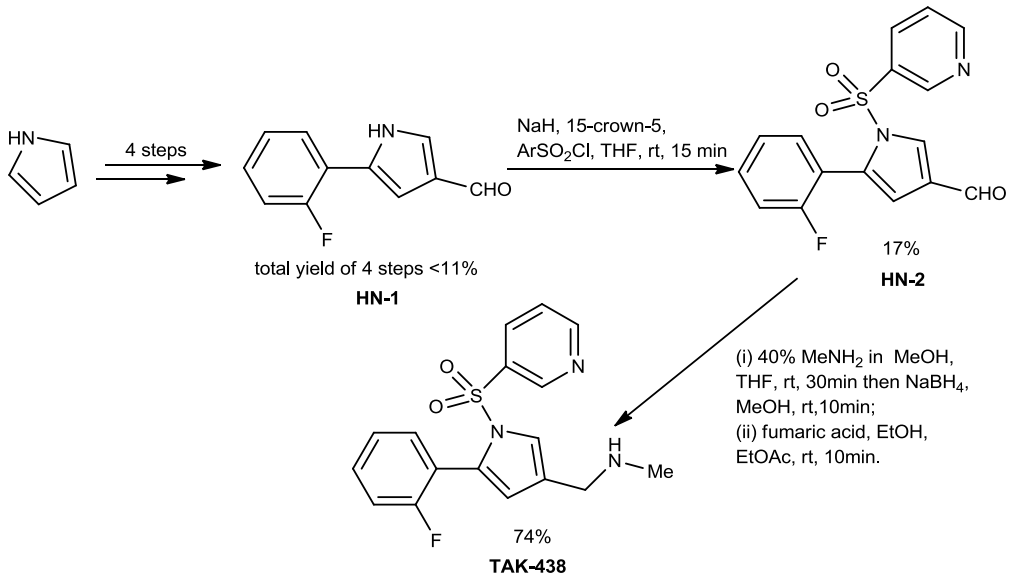
Scheme 5.10 TAK-438 and its derivatives

[158] Hori, Y.; Imanishi, A.; Matsukawa, J.; Tsukimi, Y.; Nishida, H.; Arikawa, Y.; Hirase, K.; Kajino, M.; Inatomi, N. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 231.

[159] Hori, Y.; Matsukawa, J.; Takeuchi, T.; Nishida, H.; Kajino, M.; Inatomi, N. *J Pharmacol Exp Ther*. **2011**, *337*, 797.

[160] (a)Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem*. **2012**, *55*, 4446. (b) Nishida, H.; Hasuoka, A.; Arikawa, Y.; Kurasawa, O.; Hirase, K.; Inatomi, N.; Hori, Y.; Sato, F.; Tarui, N.; Imanishi, A.; Kondo, M.; Takagi, T.; Kajino, M. *Bioorg Med Chem*, **2012,** *20*, 3925.

TAK-438 represents one of the unusual 2,4-disubstituted pyrroles which are tedious to obtain by current methods. The synthetic route to TAK-438 is outlined in Scheme 5.11. Pyrrole was converted into 5-(2-fluorophenyl)-1*H*-pyrrole-3-carb--aldehyde **HN-1** via four steps in very low total yield. In the presence of sodium hydride, sulfonylation of **HN-1** using 3-pyridine sulfonyl chloride gave **HN-2** in very low yield. Finally, the reductive amination of **HN-2** afforded TAK-438. This route is quite inefficient and room for considerable improvement exists.



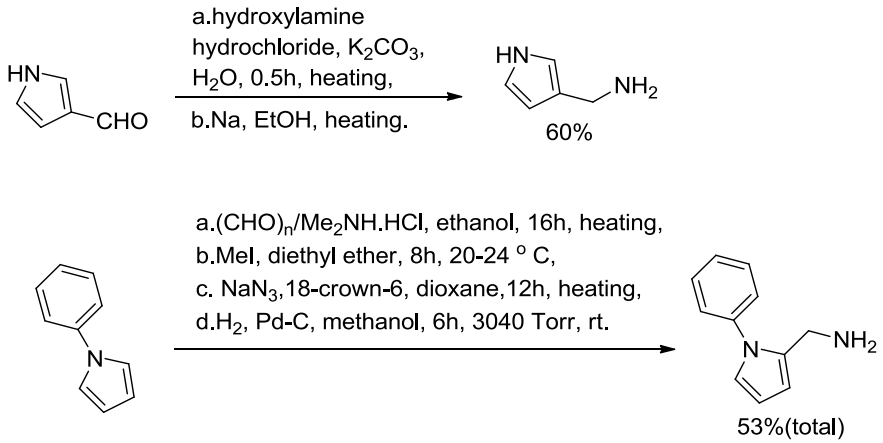
Scheme 5.11 Synthesis of TAK-438 and its derivatives

2. Methods to introduce the aminomethyl unit into pyrrole rings.

2.1. Traditional reductive amination

The current methods to access methanamine substituted pyrrole derivatives are mainly based on reductive amination of the corresponding pyrrole carboxaldehyde. For instance, the pyrrole carboxaldehyde can be converted to the oxime, which is then reduced (Scheme 5.12).[161]

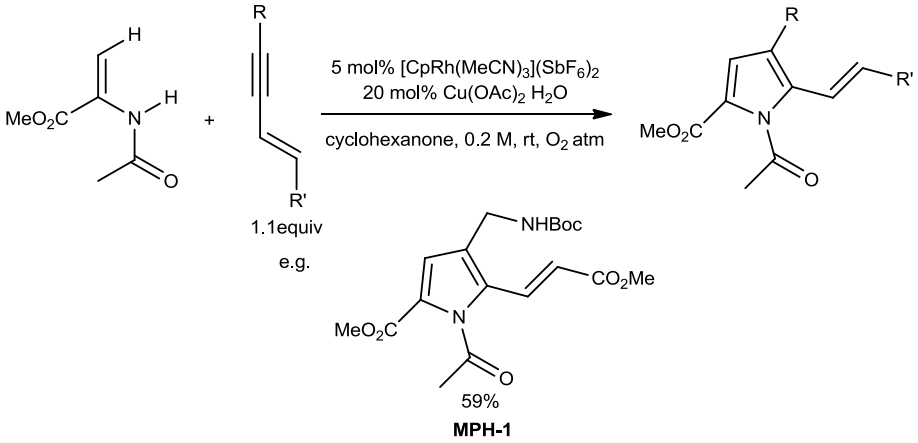
[161] (a) Korakas, D.; Varvounis, G. *Synthesis* **1994**, *2*, 164. (b) Katritzky, A. R.; Wang, J.; Yang, B. *Synth. Commun.* **1995**, *17*, 2631.



Scheme 5.12 Reductive amination

2.2. Rhodium-catalyzed pyrrole synthesis

Although, the aminomethyl group could be attached to the pyrrole ring *via* reductive amination of the carboxaldehyde precursors, they require multistep procedures to construct such pyrroles. Recently, Huestis and co-workers reported a rhodium-catalyzed approach to construct unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles from simple nitrogen-containing starting materials and incorporated the aminomethyl in one single step. But only in one case, **MPH-1**, was *tert*-butylcarbamate-protected amine present at position 3 (Scheme 5.13).[162]



Scheme 5.13 Rhodium-catalyzed pyrrole synthesis

[162] Huestis, M. P., Chan, L., Stuart, D. R., Fagnou, K., *Angew. Chem., Int. Ed.*, **2011**, *50*,1338.

III. Radical synthesis of pyrroles

The lack of a general, modular and direct synthetic protocol to construct the aminoalkyl substituted pyrrole derivatives encouraged us to design new flexible routes to pyrroles related to TAK-438 and based on xanthate chemistry.[163] As was discussed previously the xanthate radical addition-transfer process allows many hitherto difficult inter- or intramolecular addition to olefins, and these transformations may be used for the construction of many heteroaromatic compounds.[164]

1. Previous applications of xanthate chemistry in pyrrole synthesis

The synthesis of highly substituted pyrroles remains challenging and only a limited numbers of examples dealing with metal-free, modular, and direct construction of the highly substituted pyrroles have been reported in the literature.[165] Several methods for the preparation of pyrroles have been developed in our group based on the chemistry of xanthates.

1.1. Radical reaction between enesulfonamides and *α*-xanthyl ketones

In 2002, we described the route to pyrroles presented in Scheme 5.14.[166] The enesulfonamide **FW-1** was readily prepared by the reaction between ethyl pyruvate and ethylsulfonamide. The radical reaction between this enamide **FW-1** and *α*-xanthyl

---

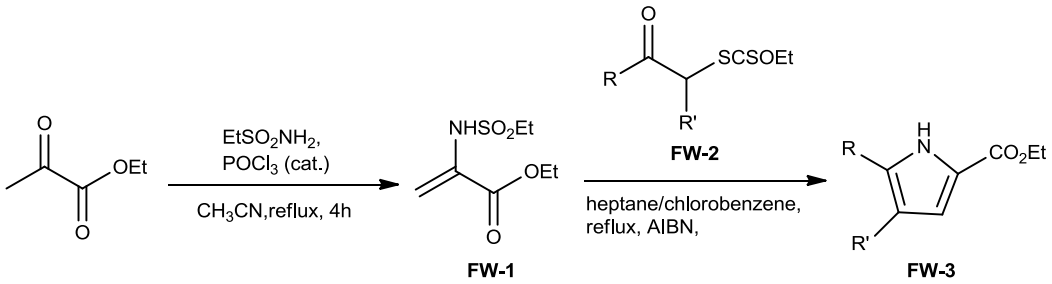
[163] (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) QuicletSire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (c) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (d) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

[164] (a) El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707. (b) Jullien, H.; Quiclet-Sire, B.; Tétart, T.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 302.

[165] (a) Zhao, M.-N.; Ren, Z. H.; Wang, Y. Y.; Guan, Z.-H. Org. Lett. **2014**, 16, 608. (b) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926.

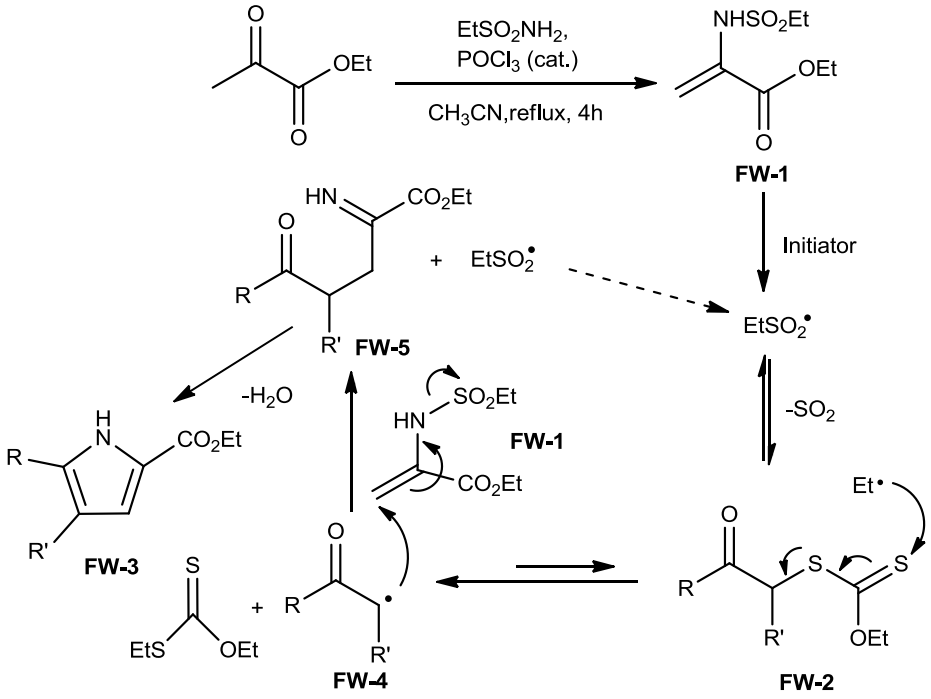
[166] Quiclet-Sire, B.; Wendeborn, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2214.

ketones **FW-2** furnished an intermediate γ-keto imine which immediately underwent an intramolecular condensation to close the ring and form the corresponding pyrroles.



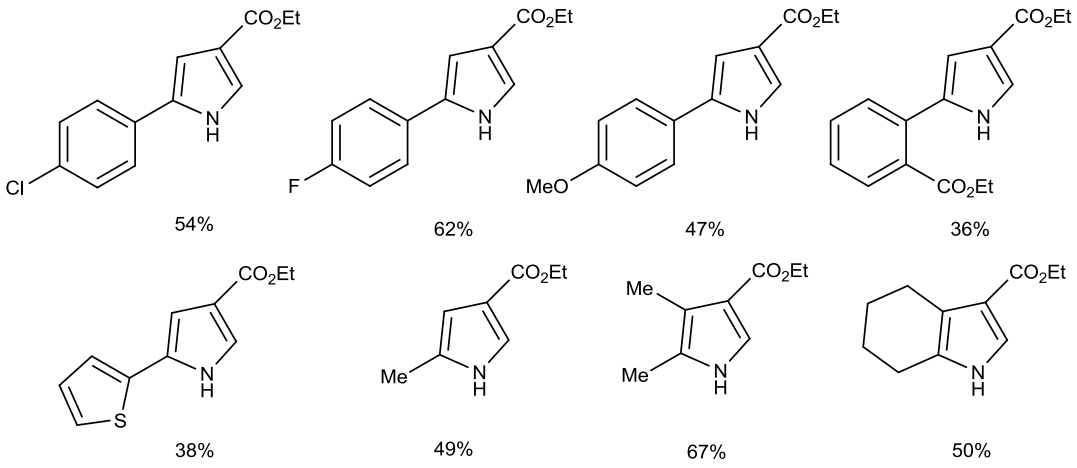
Scheme 5.14 Radical addition of enesulfonamides to α-xanthyl ketones

A plausible reaction pathway was proposed (Scheme 5.15). Under radical conditions, the addition-fragmentation on enesulfonamides **FW-1** occurs to generate an ethyl sulfonyl radical which loses sulfur dioxide to form an ethyl radical to propagate the chain. The ring closure of imine **FW-5** proceeds rapidly with loss of water to give the final pyrrole **FW-3**.



Scheme 5.15

The examples displayed in Scheme 5.16 demonstrate the tolerance for a wide range of functional groups. Furthermore, this method is ideal for accessing pyrroles bearing an ester group at position 4. However, the yields need to be improved if this method is to be applied on a large scale.

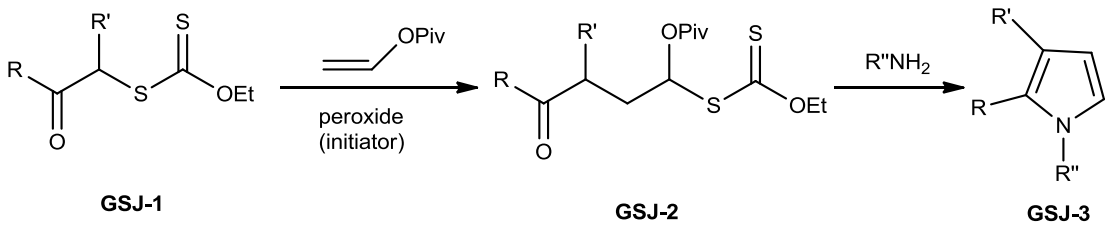


Scheme 5.16

1.2. Radical addition of *α*-xanthyl ketones to vinyl pivalate

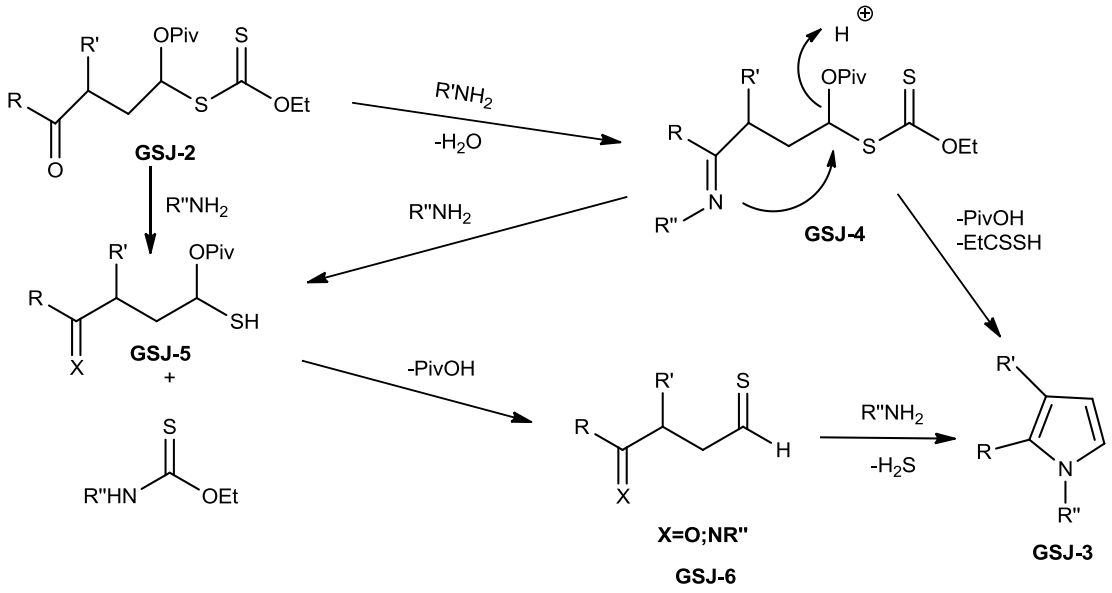
In the same year, the radical addition of *α*-xanthyl ketones to vinyl pivalate followed by aminolysis to pyrroles was described (Scheme 5.17).[167] Adducts **GSJ-2** obtained from the radical addition may be considered as the synthetic equivalents of 1,4-ketoaldehydes, which were used to form pyrroles by the Paal-Knorr reaction.

[167] Quiclet-Sire, B., Quintero, L., Sanchez-Jimenez, G., Zard, S. Z. *Synlett.* **2003**, *1*, 75.



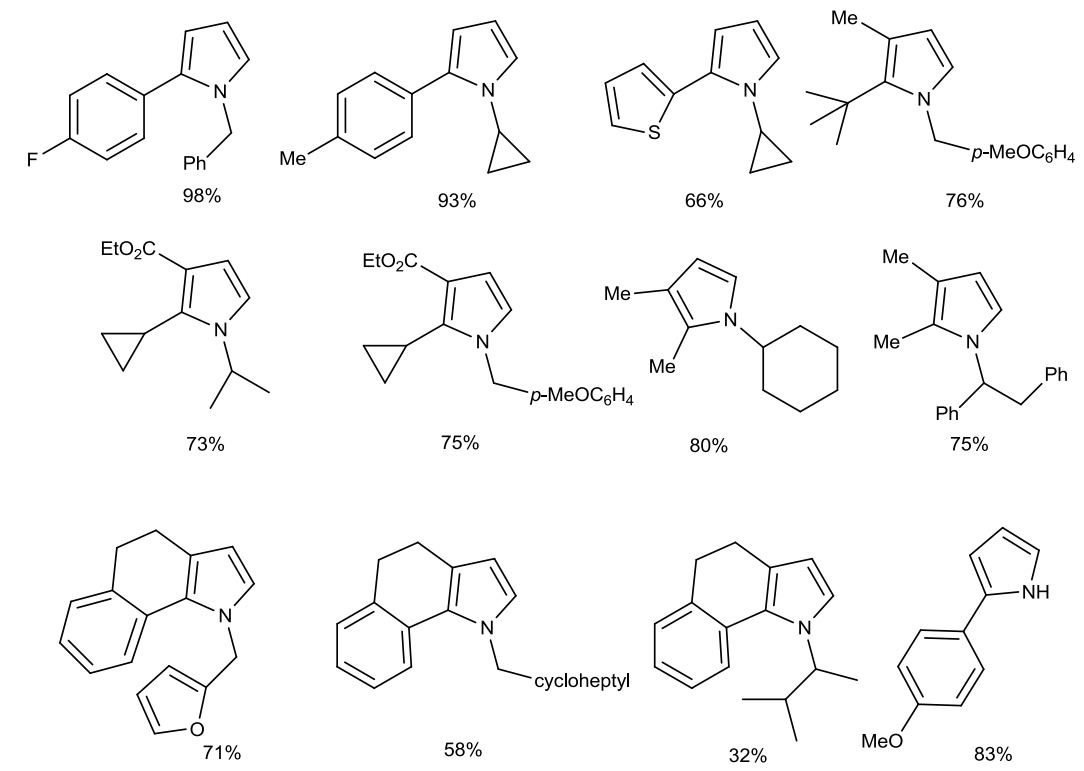
Scheme 5.17 Radical addition of α-xanthyl ketones to vinyl pivalate

Two plausible mechanistic pathways are displayed in Scheme 5.18. In the first pathway, the condensation of the amine with ketones **GSJ-2** gives the intermediate **GSJ-4** followed by its ring closure to afford the corresponding pyrrole **GSJ-3**. The second pathway derives from the possibility of aminolysis of the xanthate to give intermediate **GSJ-5** then thioaldehyde **GSJ-6** which can furnish the same pyrrole **GSJ-3** by a variety of Paal-Knorr reaction.



Scheme 5.18

The examples assembled in Scheme 5.19 indicate that 2-substituted or 2,3-disubstituted pyrroles bearing various functional groups can be readily available in generally high yield by this route.



Scheme 5.19

1.3. Radical synthesis of complex 1,4-diketones

1,4-diketones are of major importance for the synthesis of valuable heteroaromatic compounds such as thiophenes,[168] furans,[169] and pyrroles[170] via the Paal-Knorr synthetic pathway. A powerful modular approach for the preparation of complex 1,4-diketones was descried in our group, which could be applied in designing pyrrole synthesis (Scheme 5.20).[171] The radical addition of α-xanthyl ketones to 2-fluoro-6-pyridinyloxy derivatives afforded 1,4-diketones *via* an

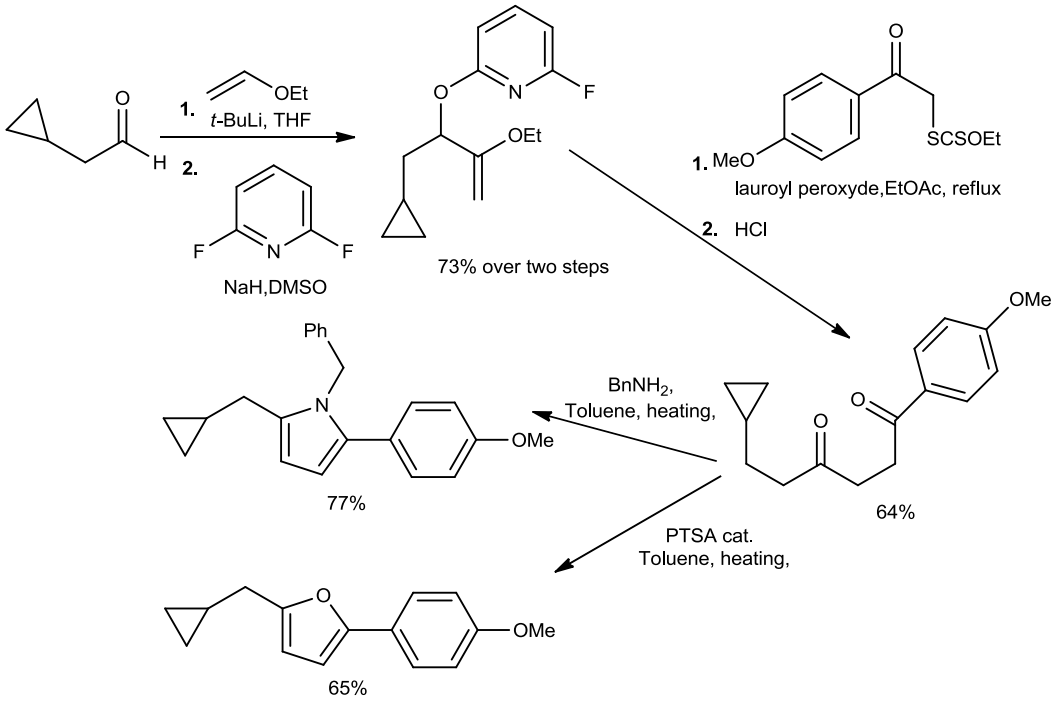
[168] Russell, R. K. In *Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds; Pergamon Press: Oxford, 1997; Vol. 2, pp 679-729.

[169] (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds;* Butterworths: London, 1963; Chapter 1, p 1. (b) Elliot, M. C. *J. Chem. Soc., Perkin Trans. I* **2002**, 2301. (c) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.

[170] (a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (b) Minetto, G.; Raveglia, L. F.; Tadde, M. *Org. Lett.* **2004**, *6*, 389. (c) Veitch, G. E.; Bridgwood, K. L.; Rands-Trevor, K.; Ley, S. V. *Synlett* **2008**, *17*, 2597.

[171] Debien, L., Quiclet-Sire, B., Zard, S. Z. *Org. Lett.* **2011**, *13*, 5676.

addition-fragmentation pathway and construction with an amine or ammonia provides the corresponding pyrroles.[172] A broad range of functional groups are tolerated in this simple process and the yields are generally high.



Scheme 5.20 Synthesis of 1,4-diketones and pyrroles

2. Pyrrole synthesis based on radical addition of various *α*-xanthyl ketones to *N*-Boc-protected azetine

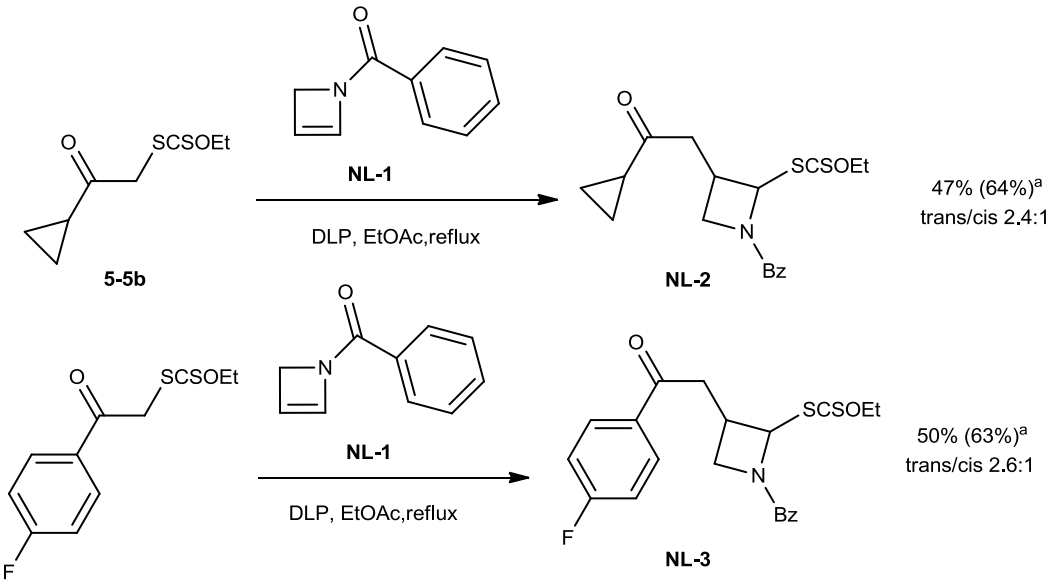
In continuation of the work on pyrrole synthesis, we adapted the approach using xanthates to access pyrroles related to TAK-438.

2.1. Synthesis of *N*-protected azetine

A few years ago, we observed that the radical addition of xanthates to various strained olefins could afford corresponding adducts in good yield.[173] A protected

[172] Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

azetine was one of the strained olefins that were examined at the time (Scheme 5.21).



[a] Yields in brackets are based on recovered starting material.

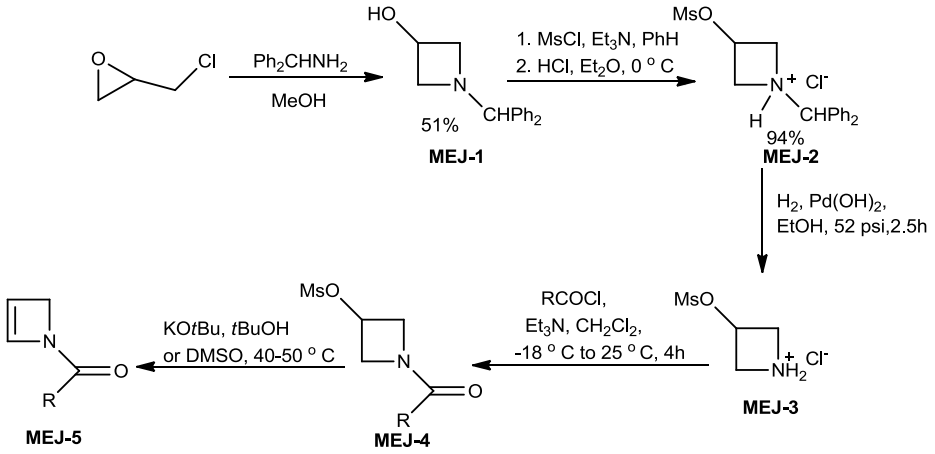
Scheme 5.21 Radical addition of xanthates to azetine

The preliminary study summarized in Scheme 5.21 encouraged us to further explore this possibility to synthesize TAK-438 type pyrroles.

In 1991, Jung and co-workers proposed an efficient synthetic route to 1-acyl-2-azetines (Scheme 5.22).[174] The nucleophilic attack on the epoxide of epichlorohydrin by benzhydrylamine gives the ring opening intermediate and then its cyclization affords the corresponding azetidine product **MEJ-1**. The sulfonylation of **MEJ-1** gives **MEJ-2**. Next, the reduction of **MEJ-2** affords **MEJ-3** which is then protected by various acyl groups to form **MEJ-4.** Finally, the elimination of its methanesulfonyl group furnishes the desired *N*-protected azetine **MEJ-5**.

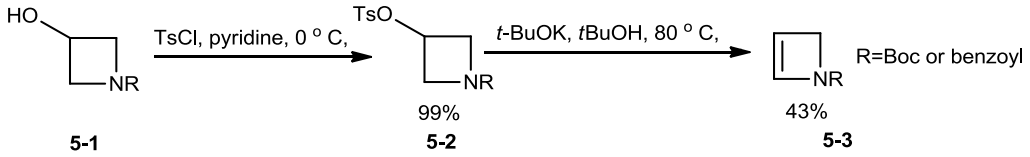
[173] Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.

[174] Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729



Scheme 5.22 Synthesis of 1-acyl-2-azetines

Since 3-hydroxyazetidine and *N*-Boc-3-hydroxyazetidine were commercially available from Fluorochem.,[175] the preparation of *N*-protected azetines now has been simplified, and the transformation of *N*-benzoyl- or *N-Boc*-3-hydroxyazetines to *N*-protected azetidines was accomplished via a sequential two step-sulfonylation and elimination (Scheme 5.23).[176]



Scheme 5.23 Synthesis of *N*-protected azetines

2.2. Radical synthesis of 2-disubstituted *N*-Boc-protected 4-aminomethyl-pyrroles

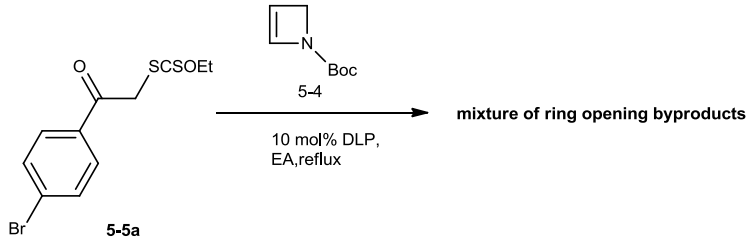
The typical radical addition of xanthates to *N*-protected azetines was then examined by us. According to the previous study, the addition of xanthates to *N*-benzoyl-azetine gave the desired adducts in moderate yield; however, under the

---

[175] 3-Hydroxyazetidine (25 g, 32 £) and *N-Boc*-3-hydroxyazetidine (25 g, 78 £).

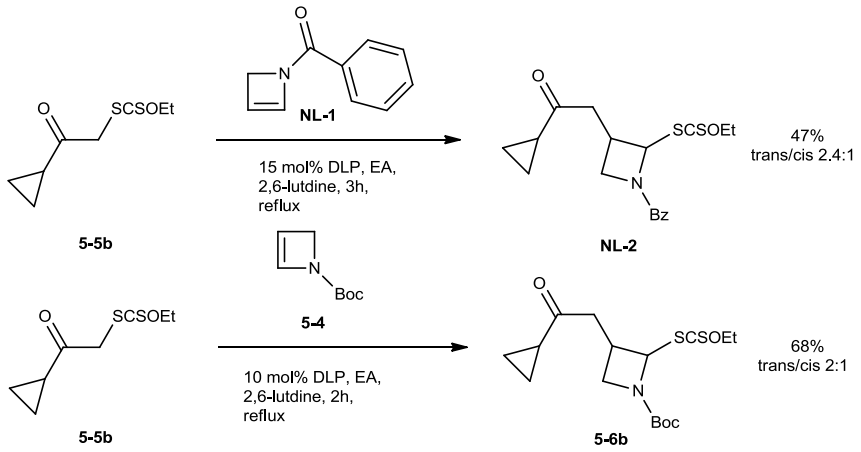
[176] McDonald, R. I., Wong, G. W., Neupane, R. P., Stahl, S. S., Landis, C. R., *J. Am. Chem. Soc.* **2010**, *132*, 14027.

same condition, the addition of xanthate **5-5a** to *N*-Boc-azetine **5-4** gave a mixture of ring opening byproducts instead of the desired adduct (Scheme 5.24). We considered that the slightly stronger basicity of *N*-Boc-azetine compared to *N*-benzoyl-azetine made the adducts more sensitive to mild acidic conditions. Thus, even a quite small amount of lauric acid formed by the decomposition of lauroyl peroxide may result in the opening of azetidine ring to release the ring strain.



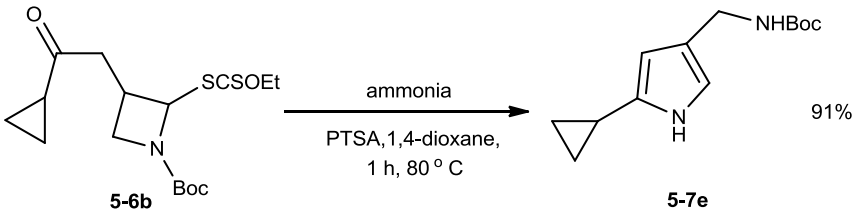
Scheme 5.24

The solution was to add some mild, hindered base such as 2,6-lutidine to the solution to neutralize the slightly acidic environment. We were delighted to observe that under these conditions the radical addition of xanthate **5-5b** to *N*-Boc-protected azetine **5-4** gave desired adduct **5-6b** in good yield (Scheme 5.25). In contrast with *N*-benzoyl-protected azetine, less DLP and a shorter reaction time was needed for the radical addition and the adduct **5-6b** was obtained in higher yield. We next examined the formation of a pyrrole from adduct **5-6b**.



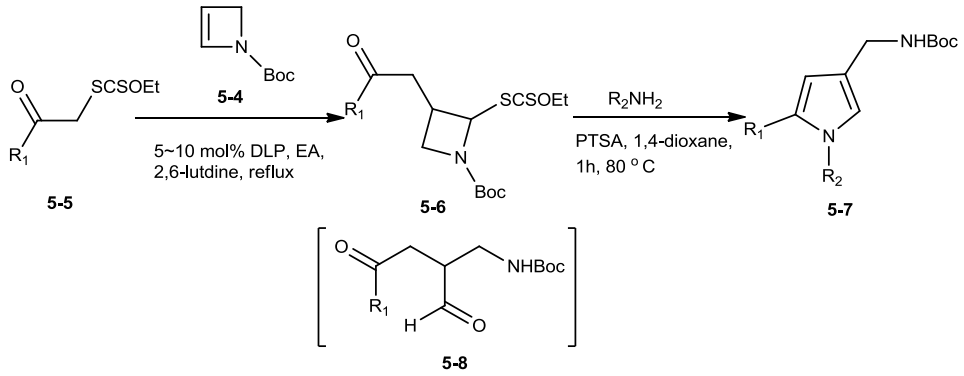
Scheme 5.25 Radical addition of xanthate **5-5b** to *N*-protected azetine

Indeed, aminolysis of **5-6b** by ammonia under similar conditions used previously resulted in the formation of desired pyrrole **5-7e** in high yield (Scheme 5.26).



Scheme 5.26 Aminolysis of adduct **5-6b**

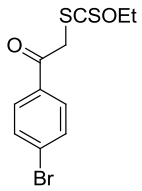
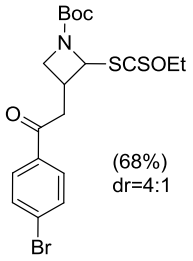
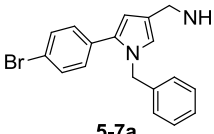
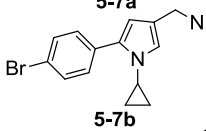
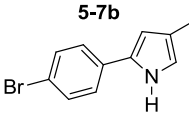
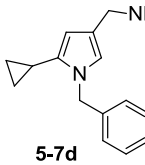
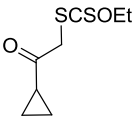
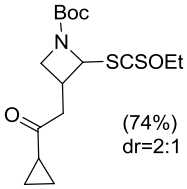
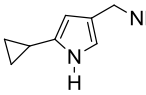
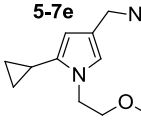
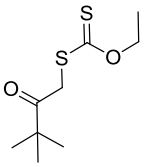
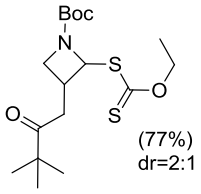
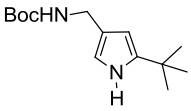
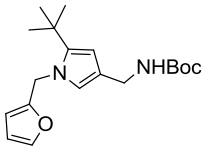
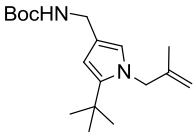
With this first success in hand, we proceeded to explore the scope of this new synthesis of pyrroles (Scheme 5.27).



Scheme 5.27 Synthesis of pyrroles **5-7** using a modular approach

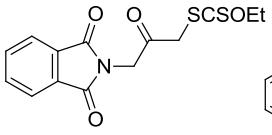
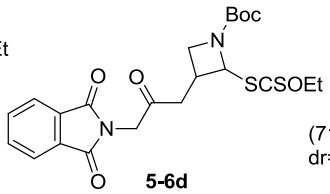
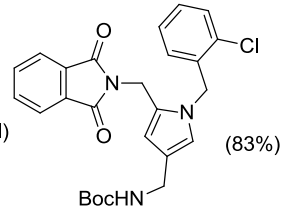
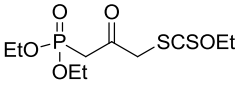
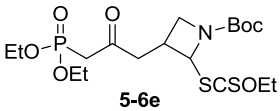
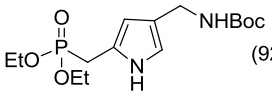
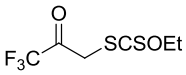
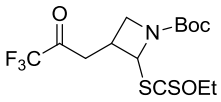
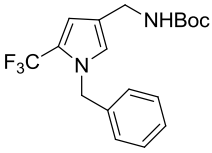
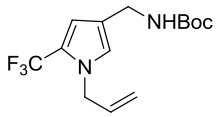
A wide range of α-ketonyl xanthates **5-5** bearing different functional groups underwent the radical addition with azetine **5-4** to afford adducts **5-6** in generally good yield, as shown by the results in Table 5.1. Treatment of the adducts with various primary amines or ammonia furnished the corresponding pyrroles **5-7** very efficiently within a short reaction time (ca 1h).

Table 5.1 Examples of pyrrole **5-7**

Xanthate **5-5**	Adduct **5-6** (yield%)[a]	Amine	Pyrrole **5-7** (yield%)
 **5-5a**	 (68%) dr=4:1 **5-6a**	benzylamine	 **5-7a** (87%)
		cyclopropylamine	 **5-7b** (93%)
		ammonia	 **5-7c** (95%)
		3,4-dichloro-benzylamine	 **5-7d** (91%)
 **5-5b**	 (74%) dr=2:1 **5-6b**	ammonia	 **5-7e** (91%)
		2-methoxyethylamine	 **5-7f** (94%)
 **5-5c**	 (77%) dr=2:1 **5-6c**	ammonia	 **5-7g** (82%)
		furfurylamine	 **5-7h** (92%)
		2-methylallylamine	 **5-7i** (88%)

[a] The dr was measured by NMR spectroscopy after purification by column chromatography.

Table 5.1 Examples of pyrrole **5-7** (continued)

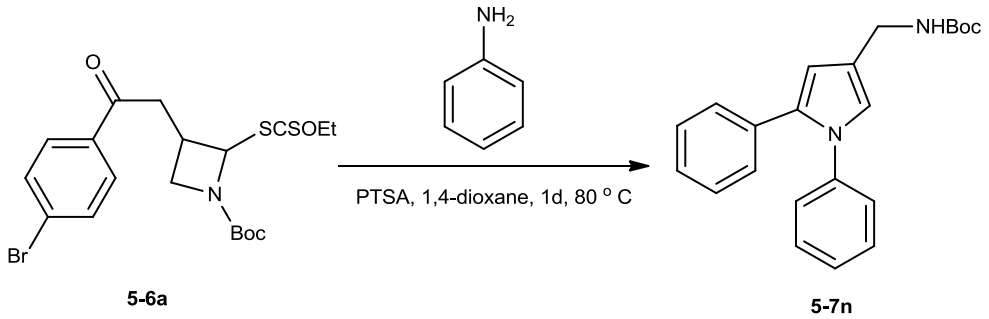
Xanthate **5-5**	Adduct **5-6** (yield%)[a]	Amine	Pyrrole **5-7** (yield%)
 **5-5d**	 **5-6d** (71%) dr=4:1	(2-chlorophenyl) methanamine	 **5-7j** (83%)
 **5-5e**	 **5-6e** (68%) dr=2:1	ammonia	 **5-7k** (92%)
 **5-5f**	 **5-6f**	benzylamine	 **5-7l** (63%)[b]
		allyamine	 **5-7m** (68%)[b]

[a] The dr was measured by NMR spectroscopy after purification by column chromatography.
[b] Over all total yield for the two steps.

The variety of the pyrroles is shown in Table 5.1. By placing various functional groups on the *α*-ketonyl xanthates, aryl, cyclopropyl, *tert*-butyl, phosphonomethyl, allyl and even trifluoromethyl groups can be incorporated into the final pyrroles. It is worth noting that pyrrole **5-7k** bearing a phosphonyl motif may further undergo the Horner–Wadsworth–Emmons reaction; the pharmacologically interesting trifluoromethyl group was easily introduced into pyrroles **5-7l** and **5-7m**. The synthesis of fluorinated pyrroles is rarely a trivial problem. In the case of pyrrole **5-7j**, two aminomethyl groups having different *N*-protecting groups are present.

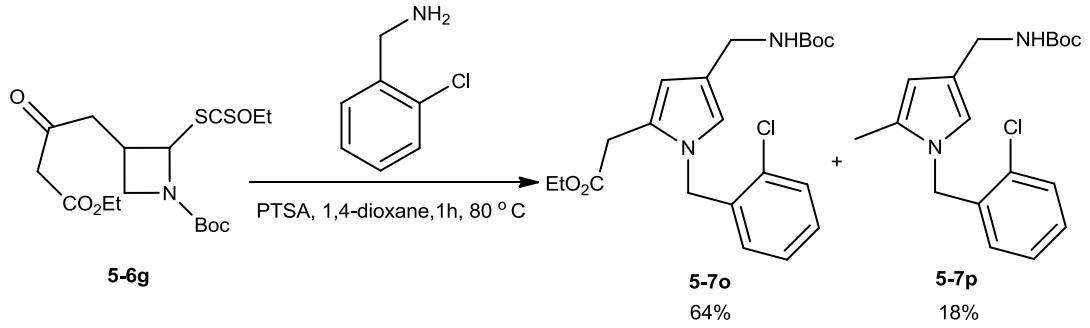
The aminolysis of xanthate group by anilines such as **5-6a** was also briefly investigated, using the same experimental conditions. However, due to the weak nucleophilicity of the aniline, only a small amount of corresponding pyrrole product

5-7n could be observed by NMR spectrum. Even after one day most of the starting material **5-6a** remained in the solution (Scheme 5.28).



Scheme 5.28 Aminolysis of **5-6a** by aniline

In the case of pyrrole **5-7o**, we found a mixture of a small amount of the desired pyrrole **5-7o** and a large quantity of byproducts which was appeared to result from aminolysis of its ester group. To minimize those byproducts, one equivalent of *p*-TsOH was added to lock the aminolysis of the ester (Scheme 5.29). The yield of pyrrole **5-7o** was significantly increased, but a small amount of pyrrole **5-7p** was also formed *via* an acid-catalyzed deethoxycarboxylation process.

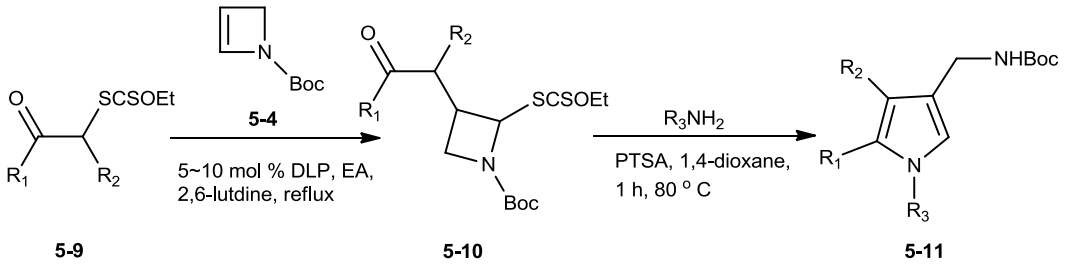


Scheme 5.29 Aminolysis of adduct **5-6g**

2.3. Radical synthesis of 2,3-trisubstituted and polycyclic *N*-Boc-protected 4-aminomethyl-pyrroles

To extend the scope of this method we used secondary *α*-ketonyl xanthates as the starting materials. The addition of secondary *α*-ketonyl xanthates **5-9** to *N*-protected

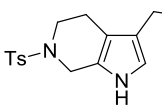
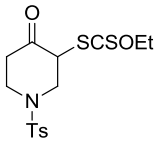
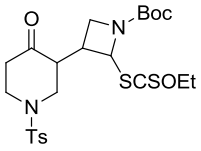
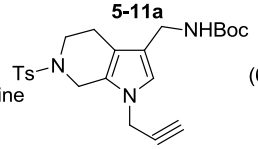
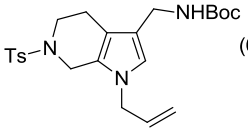
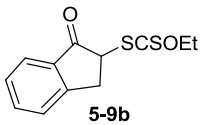
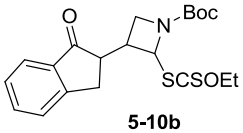
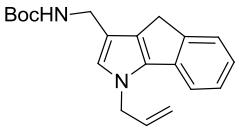
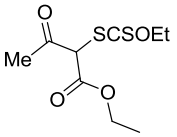
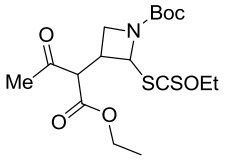
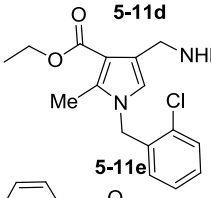
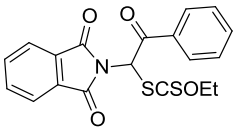
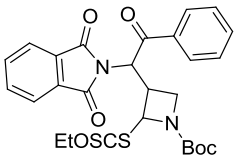
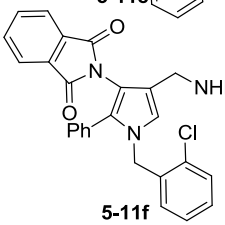
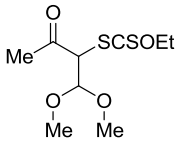
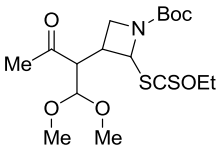
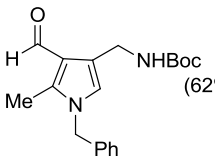
azetine **5-4** indeed afforded adducts **5-10** in high yield (Scheme 5.30 and Table 5.2). However, since this radical addition led to the formation of four diastereoisomers, the crude reaction mixture was purified by a quick filtration on silica gel to obtain the pure mixture of the four diastereoisomers which was then engaged in the next step to form the corresponding pyrroles **5-11** with the same overall efficiency.



Scheme 5.30 Synthesis of 2,3,4-trisubstituted and polycyclic pyrrole **5-11**

The examples listed in Table 5.1 are for 2,4-disubtituted pyrroles, while those in Table 5.2 are for 2,3,4-trisubstituted polycyclic pyrrole derivatives. A similar variety of functional groups may be introduced into the latter. Bicycle pyrroles such as **5-11** (**a, b, c**) with a fused six-membered including a piperidine ring and tricyclic structures were easily constructed. Under the acidic conditions, the acetal in adduct **5-10e** was cleared to afford pyrrolecarboxaldehyde **5-11g** directly. This interesting pyrrole could in principal be elaborated into a more complex 3,4-bis-(aminomethyl)pyrroles by reductive amination. Alternatively, the aldehyde may be condensed with the amino group already present following removal of the protecting Boc group. In pyrrole **5-11f**, a phthalimide protected amino unit is directly attached onto the ring. Very few methods allow the synthesis of amino pyrroles, which are almost invariably obtained by reduction of the corresponding nitropyrrole. Furthermore, in contrast with sensitive free amino pyrroles, the electron-withdrawing phthalimido a motif protects the pyrrole against aerial oxidation.

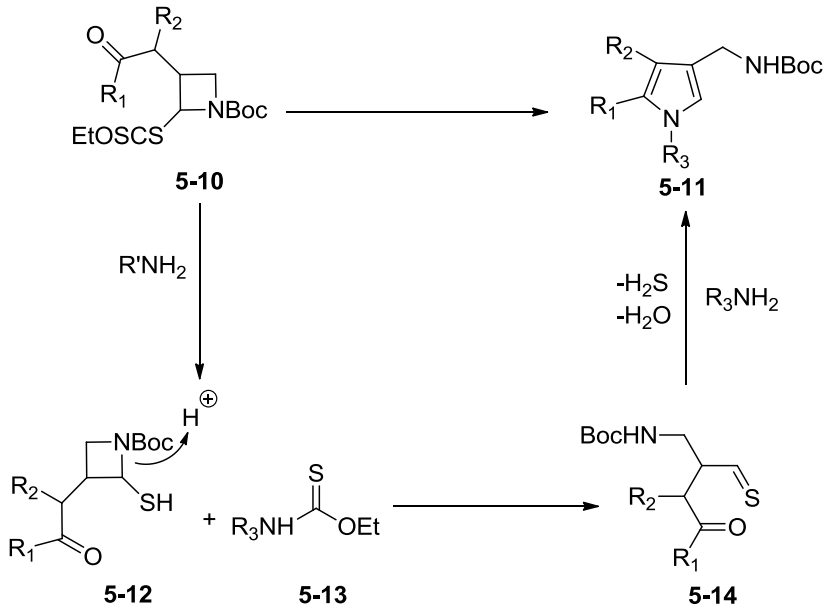
Table 5.2 Examples of Pyrrole **5-11**

Xanthate **5-9**	Adduct **5-10**[a]	Amine	Pyrrole **5-11** (yield%)[b]
		ammonia	 **5-11a** (67%)
 **5-9a**	 **5-10a**	mono-propargylamine	 **5-11b** (66%)
		allylamine	 **5-11c** (63%)
 **5-9b**	 **5-10b**	allylamine	 **5-11d** (68%)
 **5-9c**	 **5-10c**	(2-chlorophenyl) methanamine	 **5-11e** (61%)
 **5-9d**	 **5-10d**	(2-chlorophenyl) methanamine	 **5-11f** (58%)
 **5-9e**	 **5-10e**	Benzylamine	 **5-11g** (62%)

[a] The crude adducts were used directly in second step after a quick purification on silica gel. [b] The total yield of step 1 and step 2.

A plausible mechanism for the pyrrole formation is outlined in Scheme 5.31. Aminolysis of the xanthate leads to the formation of thiol **5-12** and thiocarbamate **5-13**, which in some cases could be isolated. Next, due to the strain of the azetidine

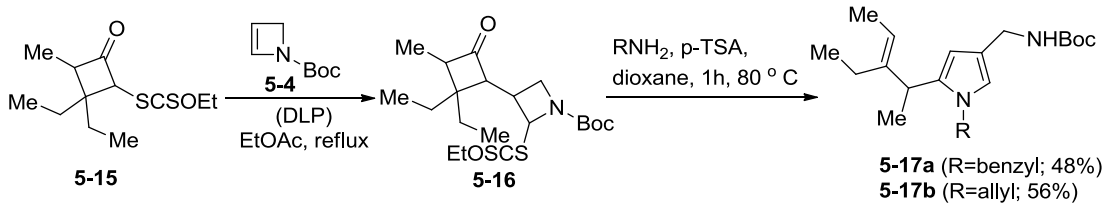
ring thiol **5-12** readily undergoes ring opening to form thioaldehyde **5-14**. Finally, since thioaldehyde **5-14** bearing a thiocarbonyl and a carbonyl groups, its condensation with primary amines or ammonia gives the corresponding pyrrole **5-11** by a similar pathway to the one involved in the Paal-Knor reaction.



Scheme 5.31 Mechanism of pyrrole formation

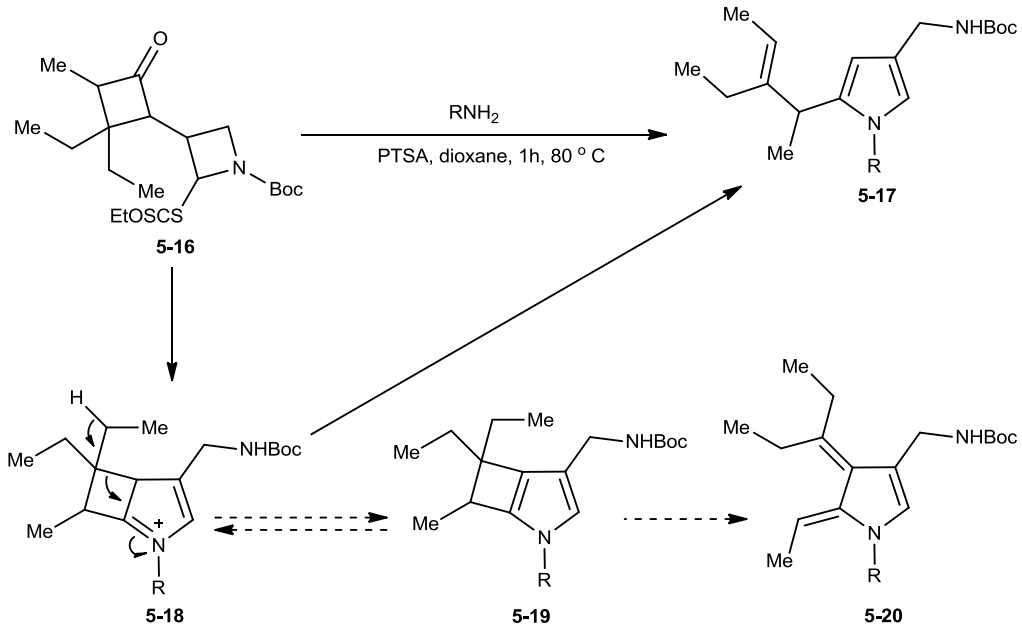
We attempted to prepare a pyrrolocyclobutanone using the same approach. Only two cases for the synthesis of such pyrroles had been reported so far.[177] The radical addition of xanthate **5-15** to **5-4** proceeded normally to give **5-16** by further aminolysis with two different amines furnished unexpected pyrroles **5-17a** and **5-17b**, where the cyclobutane ring had been broken (Scheme 5.32).

[177] (a) Buhr, G. *Chem. Ber.* **1973**, *106*, 3544. (b) Yamasaki, K.; Saito, I.; Matsuura, T. *Tetrahedron Lett.* **1975**, *16*, 313. One diene of type 11 has been generated and captured via a Diels−Alder cycloaddition: (c) Janicki, S. Z.; Petillo, P. A.; Vessels, J. T. *Org. Lett.* **2000**, *2*, 73.



Scheme 5.32 Synthesis of pyrroles **5-17**

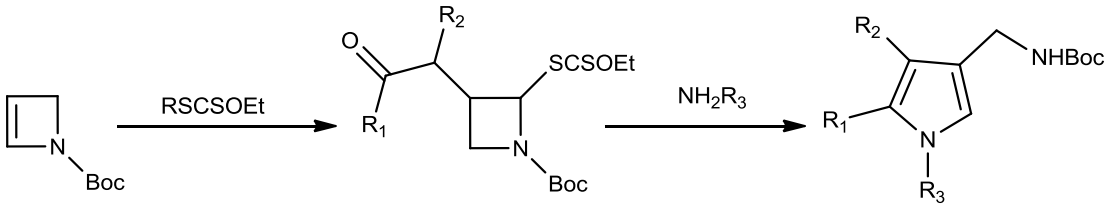
A plausible explanation is that upon treatment of adduct **5-16** with the primary amine and *p*-toluenesulfonic acid, a cyclic intermediate **5-18** is indeed formed, but the strain inherent in the pyrrolocyclobutanone structure force the reaction to proceed by ring opening of the cyclobutane in the final aromatization step leading to pyrrole **5-17**, as shown in Scheme 5.33. It is not clear if intermediate **5-18** exists in the medium in equilibrium with the aromatic pyrrole **5-19**, the latter could in principle undergo an electrocyclic ring opening to give **5-20**, but no products derived from such an intermediate were observed.



Scheme 5.33 Mechanism for the formation of pyrrole **5-17**

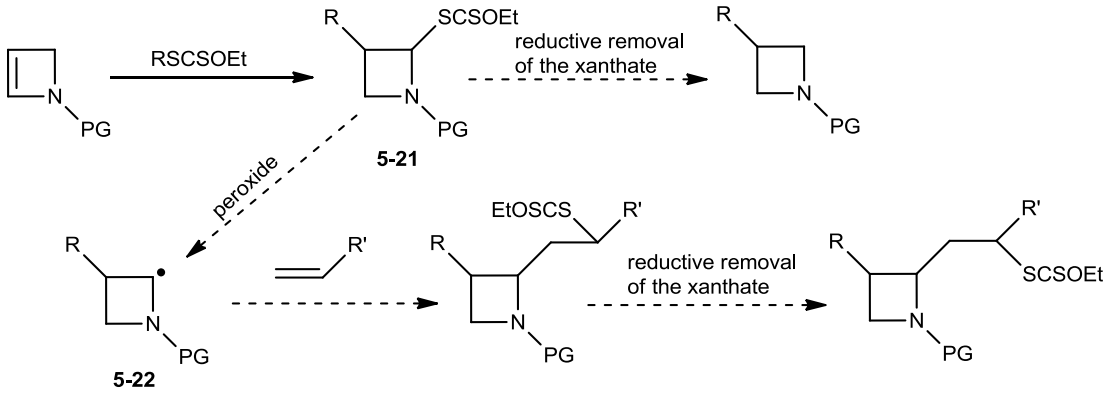
Conclusion

In summary, we have established a flexible, convergent route for the synthesis of diversely substituted pyrroles related to TAK-438. This two-step modular procedure generalized in Scheme 5.34 represents a practical approach to quickly combine these components into a pyrrole structure. Almost any functional group could be incorporated either through the xanthate partner or through the amine moiety. Most of the pyrroles obtained in the present study would be tedious to prepare by other routes based on ionic or organometallic pathways.



Scheme 5.34

Two possible extensions of this approach are outlined in Scheme 5.35. Reductive removal of the xanthate group from adducts **5-21** leads to variously functionalized azetidine derivatives which are gaining importance in medicinal chemistry. The addition of intermediate xanthate **5-21** to another olefin would also be interesting. This has not yet been attempted but may require changing the protecting group to tune the stability of the intermediate radical **5-22**. In addition to providing a better understanding of the influence of the substituents on the nitrogen on the stability of the radicals, such an extension would open access to highly substituted azetidine derivatives.


RSCSOEt
R
SCSOEt
reductive removal
of the xanthate
N
PG
5-21
peroxide
5-22
R'
EtOSCS
reductive removal
of the xanthate

Scheme 5.35

Experimental Part

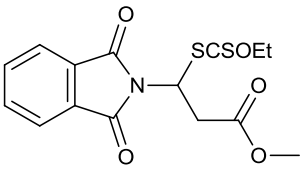
General Experimental Methods

Anhydrous dichloromethane was obtained by distillation from calcium hydride under nitrogen. Anhydrous THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl under nitrogen. Other solvents were used as supplied by commercial sources. Petroleum ether refers to the fraction of light petroleum ether, boiling between 40-60 ℃. Purification procedures were in accordance with the instructions in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Fourth Edition, The Bath Press, Bath, 2002. All reactions were carried out under dry, oxygen free nitrogen. Flash chromatography was performed on silica gel (SDS, 60 Å C. C. 40-63 μm) as the stationary phase. Thin Layer Chromatography (TLC) was performed on aluminum plates pre-coated with silica gel (Merck silica gel, 60 F_{254}), which were visualized by the quenching of UV fluorescence when applicable (λ_{max} = 254 nm and/or 366 nm) and/or by staining with anisaldehyde or vanillin in acidic ethanol followed by heating. When compounds could not be visualized with anisaldehyde or vanillin, a solution of phosphomolybdic acid in ethanol or a potassium permanganate aqueous solution were used. Infrared spectra were recorded as solutions in $CDCl_3$ using CaF_2 cells, on a Perkin-Elmer FT 1600 or FT 2000. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported. Magnetic resonance spectra were recorded at ambient temperature on either a Bruker AMX 400, or a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz. The following abbreviations were utilized to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz. Chemical shifts (δ_H, δ_C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak ($CDCl_3$: δ_H = 7.26 and δ_C = 77.0). High-resolution mass spectra were recorded by positive electron impact ionization (EI+) at 70 eV on a JEOL JMS-GCmate II mass

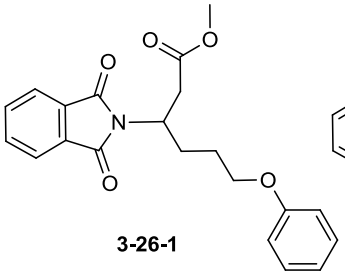
spectrometer. The quoted masses are accurate to ± 5 ppm. DLP corresponds to di-lauroyl peroxide (often sold under lauroyl peroxide or laurox).

Molecules cited in the experimental part

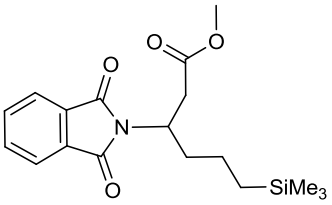
Molecules of chapter 3



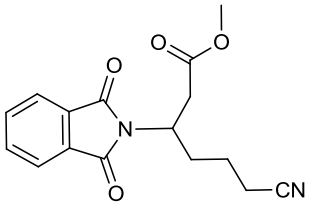
3-25



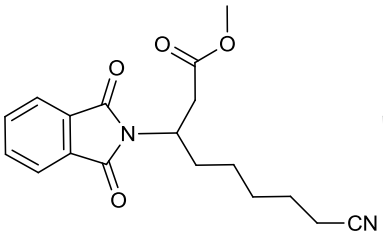
3-26-1



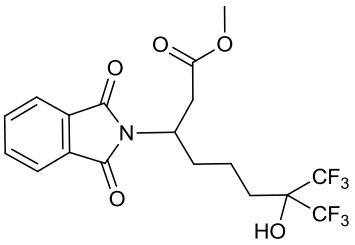
3-26-2



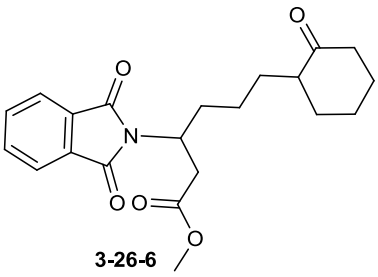
3-26-3



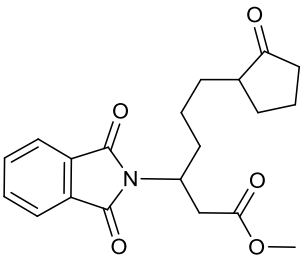
3-26-4



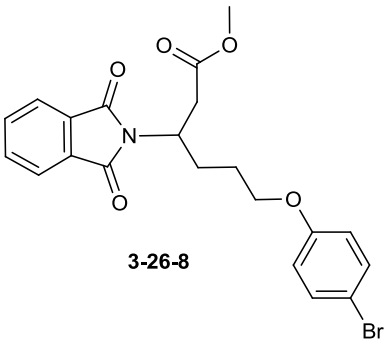
3-26-5



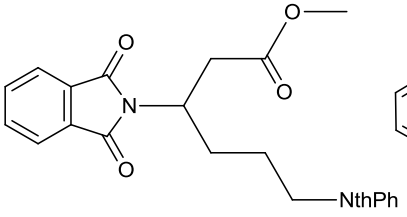
3-26-6



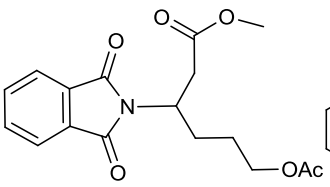
3-26-7



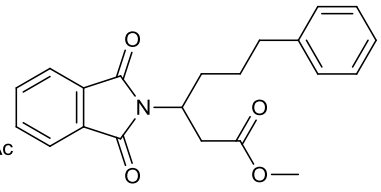
3-26-8



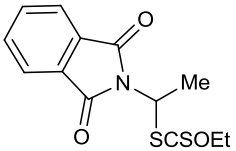
3-26-9



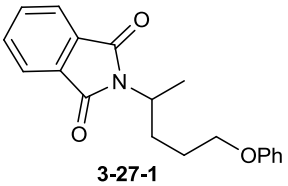
3-26-10



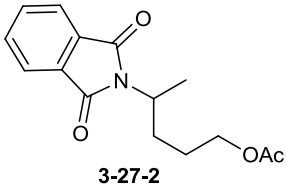
3-26-11



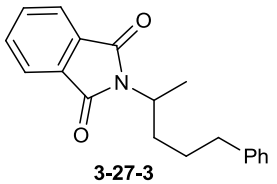
3-27



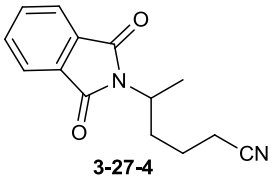
3-27-1



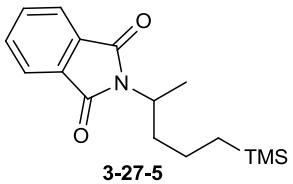
3-27-2



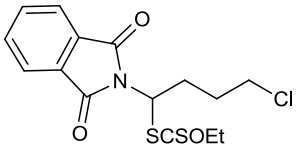
3-27-3



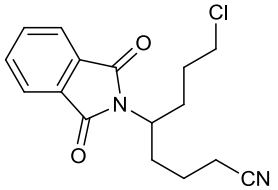
3-27-4



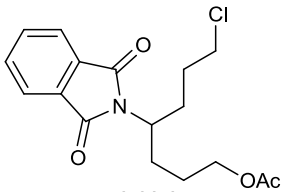
3-27-5



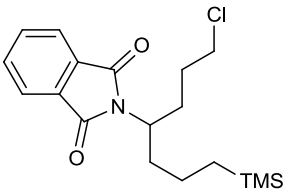
3-30



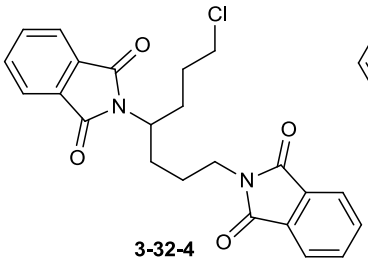
3-32-1



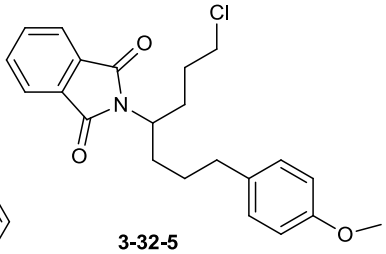
3-32-2



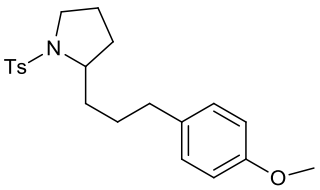
3-32-3



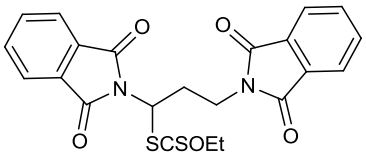
3-32-4



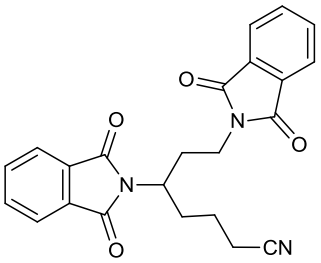
3-32-5



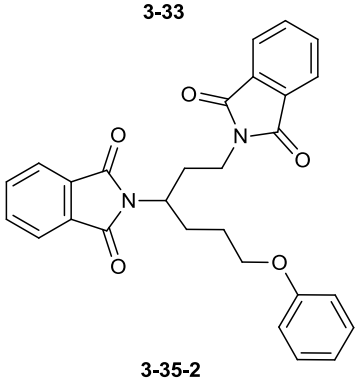
3-33



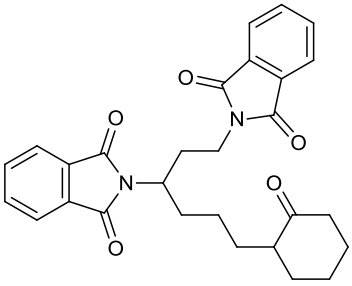
3-34



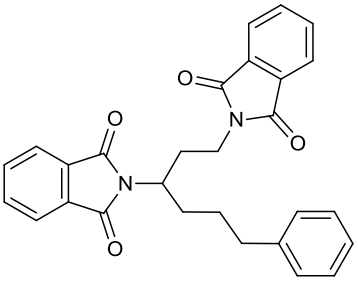
3-35-1



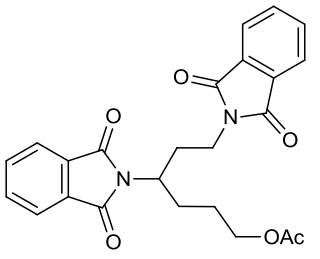
3-35-2



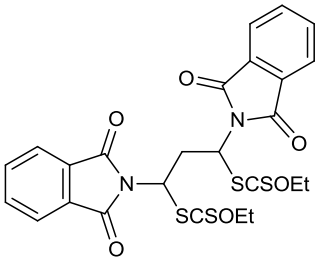
3-35-3



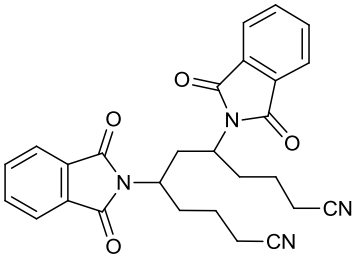
3-35-4



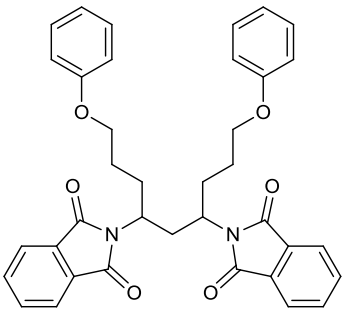
3-35-5



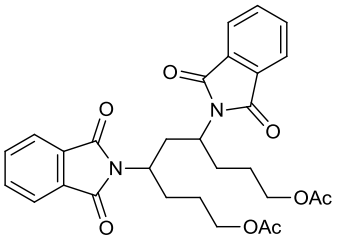
3-36



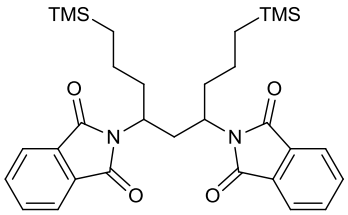
3-37-1



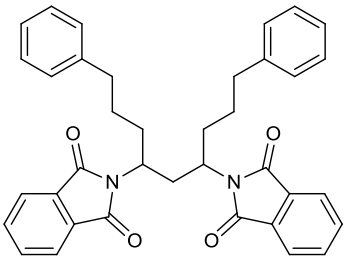
3-37-2



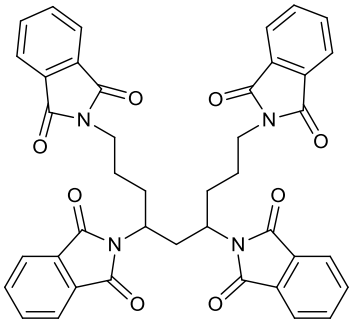
3-37-3



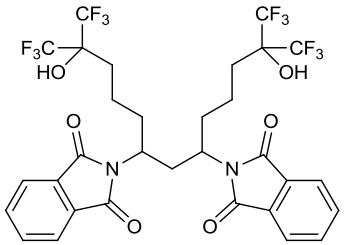
3-37-4



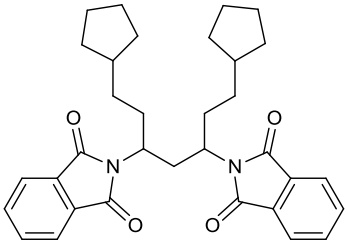
3-37-5



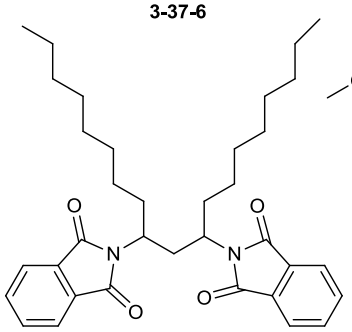
3-37-6



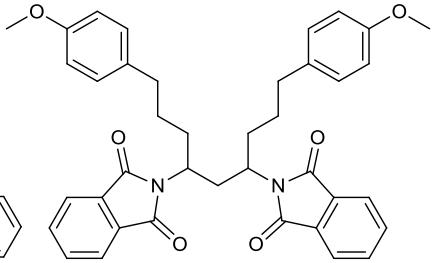
3-37-7



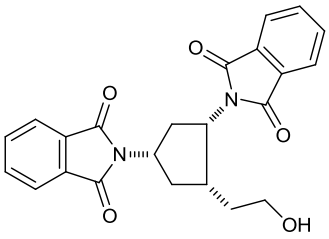
3-37-8



3-37-9

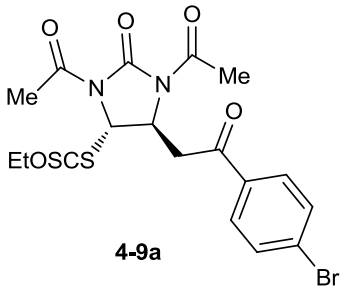


3-37-10

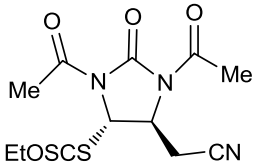


3-40

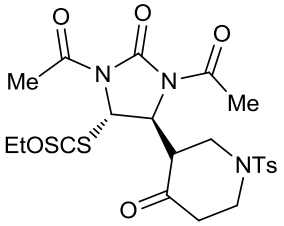
Molecules of chapter 4



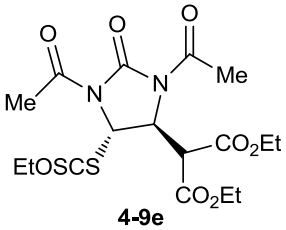
4-9a



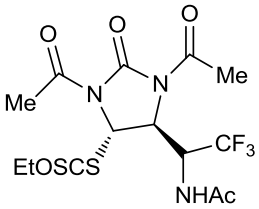
4-9b



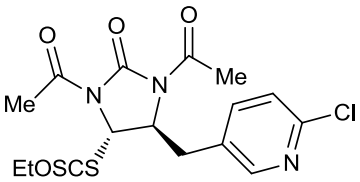
4-9c



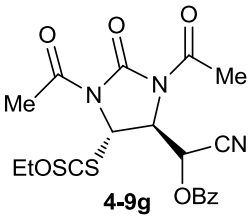
4-9e



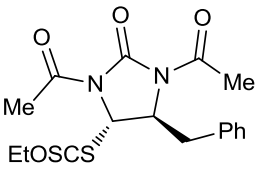
4-9d



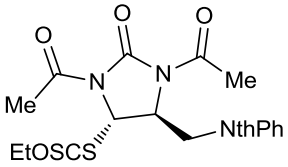
4-9f



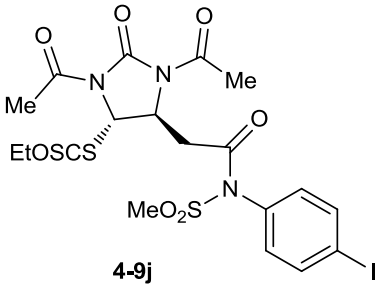
4-9g



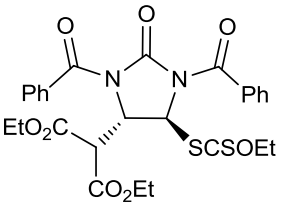
4-9h



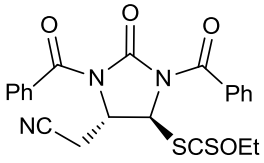
4-9i



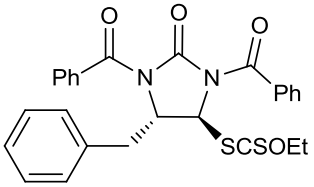
4-9j



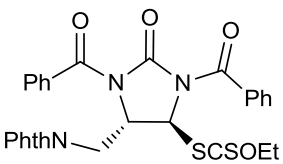
4-11a



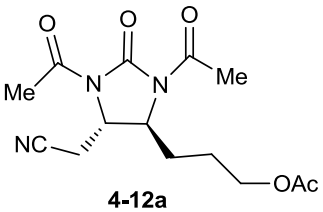
4-11b



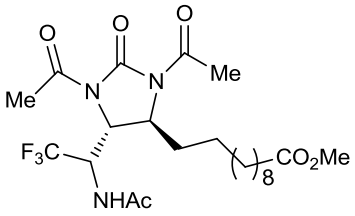
4-11c



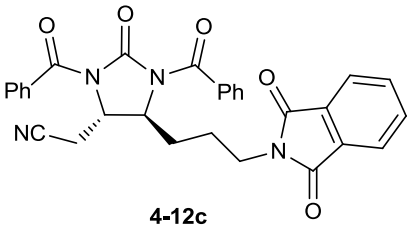
4-11d



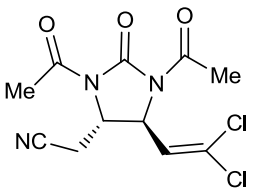
4-12a



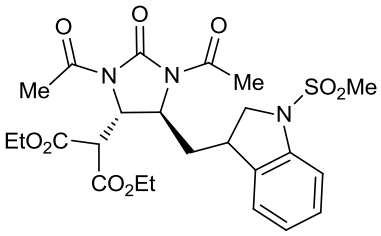
4-12b



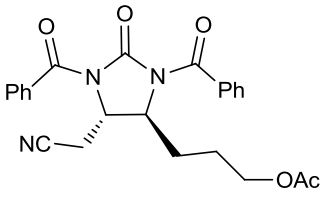
4-12c



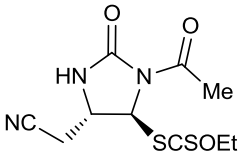
4-13



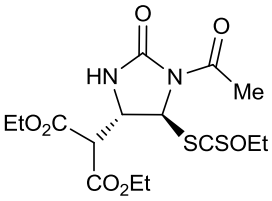
4-15



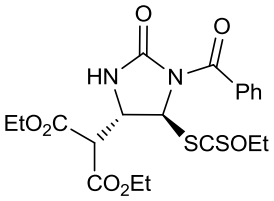
4-18



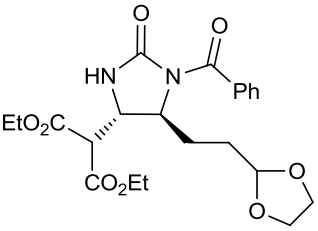
4-21



4-22

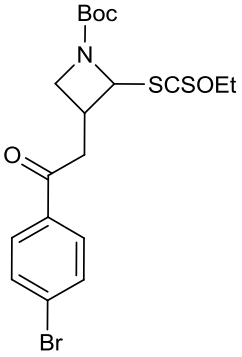


4-23

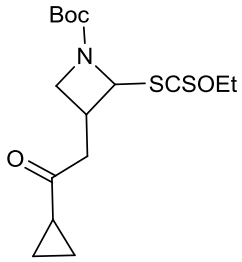


4-24

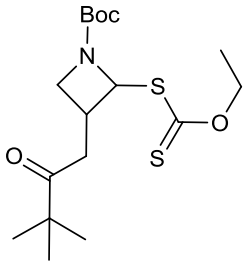
Molecules of chapter 5



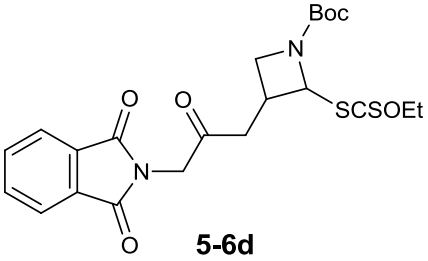
5-6a



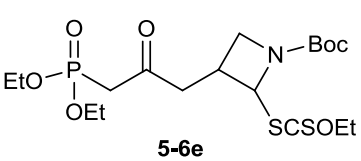
5-6b



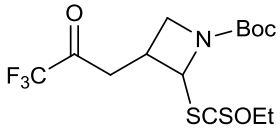
5-6c



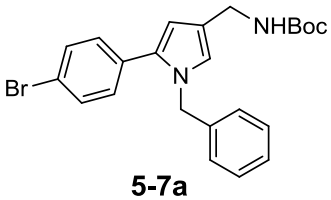
5-6d



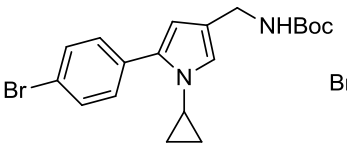
5-6e



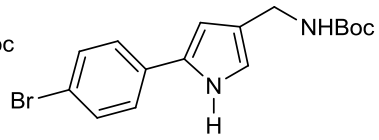
5-6f



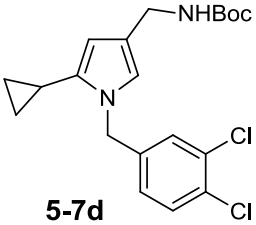
5-7a



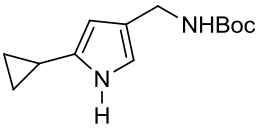
5-7b



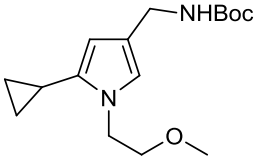
5-7c



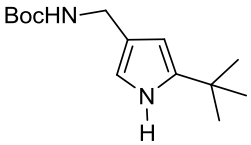
5-7d



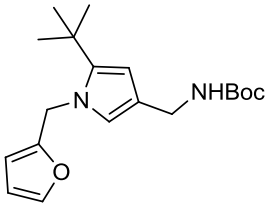
5-7e



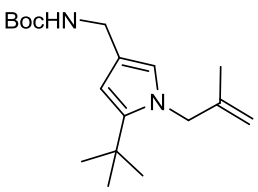
5-7f



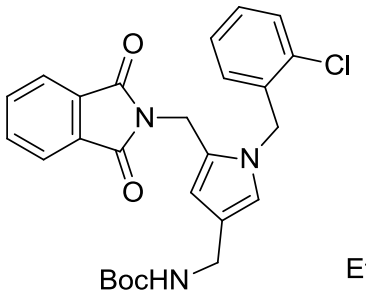
5-7g



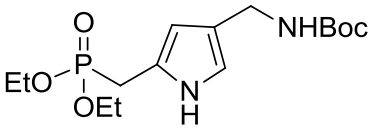
5-7h



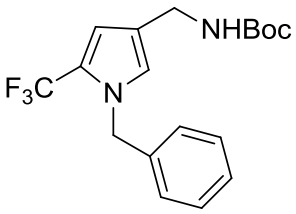
5-7i



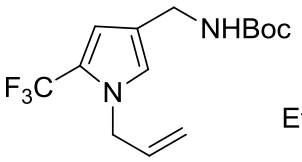
5-7j



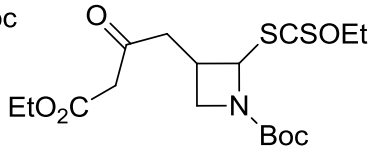
5-7k



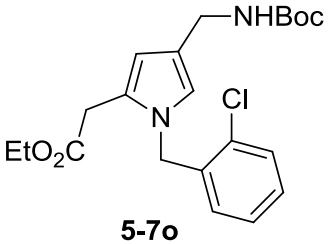
5-7l



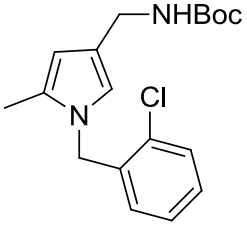
5-7m



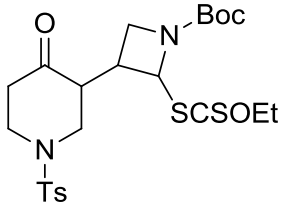
5-6g



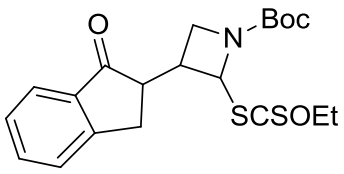
5-7o



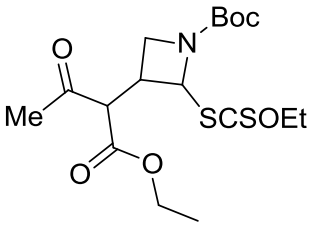
5-7p



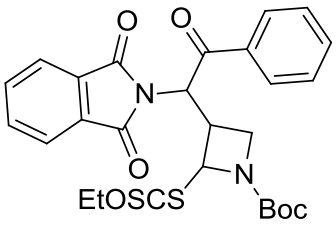
5-10a



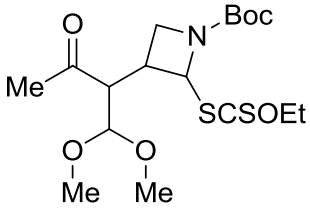
5-10b



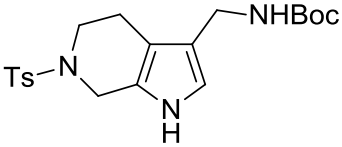
5-10c



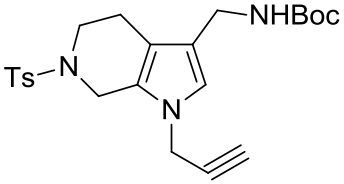
5-10d



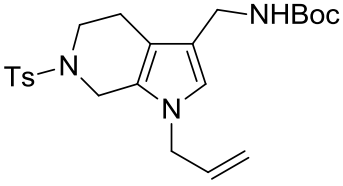
5-10e



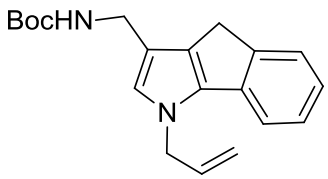
5-11a



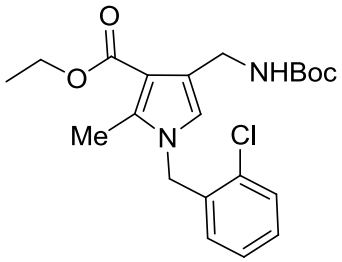
5-11b



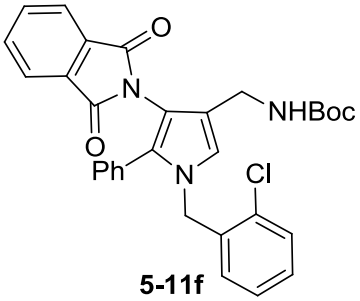
5-11c



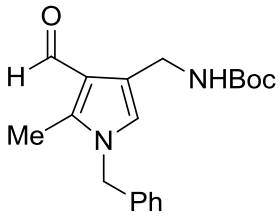
5-11d



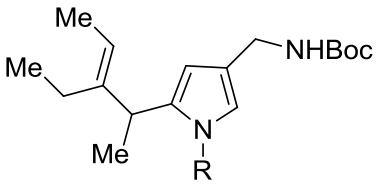
5-11e



5-11f



5-11g



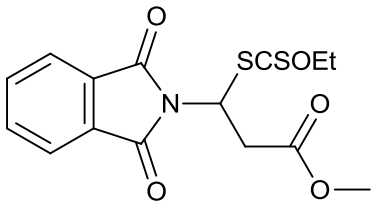
5-17a (R=benzyl)
5-17b (R=allyl)

Chapter 3

General procedure A for radical addition: A magnetically stirred solution of xanthate (1 equiv) and olefin (1.5 equiv to 3.0 equiv) were dissolved in ethyl acetate (1 ml/mmol of xanthate) was refluxed for 15 min. DLP (5 mol%) was then added and additional DLP (5 mol%) was added every 60 min until total consumption of xanthate. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was either engaged in a new reaction or purified by flash chromatography on silica gel to yield the desired compounds.

General procedure B for reduction: The residue was dissolved in dioxane (10 mL/mmol) then triethylamine (3.3 equiv.) and a solution of H_3PO_2 50% in water (3 equiv.) were added. The solution was refluxed for 15 min and AIBN (10%mol) was then added. After 1 hour, the solution was allowed to cool to room temperature, water and ethyl acetate were added. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to yield the desired compounds.

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-ethoxythiocarbonylsulfanyl-propionic acid methyl ester (3-25)



3-25

Phthalimide (30 g, 0.21mol) and methyl acrylate (28.2 ml, 0.3 mol) with DBU (15.6 ml, 0.1 mmol) were stirred in acetonitrile (100 ml) at room temperature for 2 hours. The reaction mixture was then concentrated under reduced pressure and poured into petroleum ether to get a solid which was washed with water to yield pure product

3-22 (45.4 g, 94%). **3-22** (2.1 g, 9.00 mmol), NBS (1.92 g, 10.08 mmol) in CCl_4 (150 ml) was heated at reflux under nitrogen for 5 h; the reaction was initiated by irradiation with a 300 W lamp. The reaction mixture was then cooled, filtered and washed with sodium thiosulfate. After extracting the solution with DCM, the organic layer was concentrated under reduced pressure to yield 2.3 g product **3-23** (83%) without further purification. **3-23** (2.3 g, 7.5 mmol) was dissolved in acetone (2 ml per mmol). Under a nitrogen atmosphere KSCSOEt (1.3 g, 8 mmol) was added portion wise over a period of five minutes. It was then left to stir for a further twenty minutes before the acetone was evaporated off under reduced pressure. The residue was then taken up in DCM/H_2O and extracted. The DCM layers were dried over Na_2SO_4 before being filtered and evaporated under reduced pressure to yield the crude xanthate. This was then purified by column chromatography using petroleum ether: ethyl acetate, 25:1~10:1 v/v, to obtain 2.1 g **3-25** as a pale yellow oil in 80% yield.

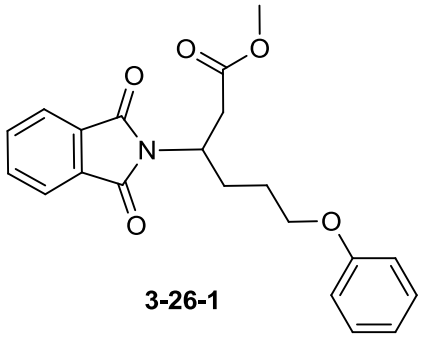
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.91-7.85 (m, 2H, CHPhth), 7.77-7.72 (m, 2H, CHPhth), 6.65 (dd,1H, J = 5.5 Hz, J =10.2 Hz, CHS), 4.67 (dq, 2H, J = 1.0 Hz, J = 7.1 Hz, -OC*H*$_2$CH$_3$), 3.66 (s, 3H, CO_2CH_3), 3.49 (dd, 1H, J = 10.2 Hz, J = 16.5 Hz CHSC*H*H), 3.16 (dd, 1H, J = 5.5Hz, J = 16.5 Hz, CHSCH*H*), 1.44 (t, 3H, J = 7.1 Hz, -OCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 209.7 (C=S), 169.4 (C=O), 166.5 (C=O), 134.4 (CPhth), 131.6 (CPhth), 123.7 (CPhth), 70.6 (O*C*H$_2$C*H*$_3$), 53.2 (CHS), 52.2 (CO_2*C*H$_3$), 37.2 (CH_2), 13.7 (OCH$_2$*C*H$_3$);

IR (CCl_4): ν max 2963, 1780, 1726, 1555, 1377, 1226, 1051;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{15}NO_5S_2$: 353.0392 (353.0391).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-phenoxy-hexanoaic acid methyl ester (3-26-1)



3-26-1

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and allyl phenyl ether (86 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 120 mg **3-26-1** (yield: 78%) as a pale yellow oil.

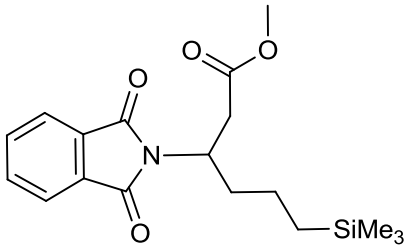
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.79 (2H, m, CHPhth), 7.76-7.68 (m, 2H, CHPhth), 7.27-7.18 (m, 2H, Ar), 6.90 (t, 1H, J=7.3Hz, Ar), 6.83 (d, 2H, J=7.9Hz, Ar), 4.76-4.66 (1H, m, NCH), 3.94 (t, 2H, J=6.1Hz), 3.60 (s, 3H, CO_2CH_3), 3.21 (dd, 1H, J=9.5Hz, J=16.1Hz, CH*H*CO_2Me), 2.82 (dd, 1H, J=5.3Hz, J=16.1Hz, C*H*HCO_2Me), 2.31-2.18 (m, 1H), 1.98-1.90 (m, 1H), 1.78-1.69 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.9 (C=O), 168 (C=O), 158.5 (Cq-O), 133.8, (CPhth), 131.4 (CqPhth), 129.1 (Ar), 123 (CPhth), 120.3 (Ar), 114.1 (Ar), 66.5 (-*C*H_2OPh), 51.5 (CO_2*C*H_3), 47.5 (NCH), 36.4 (*C*H_2CO_2), 28.6 (NCH*C*H_2), 25.9 (CH_2);

IR (CCl_4): νmax 1777, 1746, 1721, 1245, 1201, 1174, 1006;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{21}NO_5$: 367.1420 (367.1421).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-(trimethylsilyl)-hexanoic acid methyl ester (3-26-2)



3-26-2

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and allyl trimethylsilane (96 mg, 0.84 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 96 mg **3-26-2** (yield: 66%) as a colorless oil.

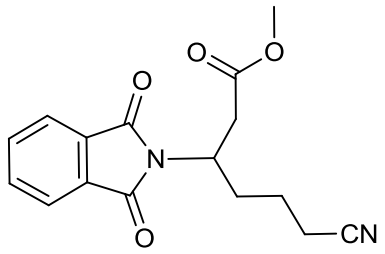
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.78 (m, 2H, CHPhth), 7.75-7.66 (m, 2H, CHPhth), 4.71-4.64 (1H, m, NCH), 3.59 (s, 3H, CO_2CH_3), 3.16 (dd, 1H, J=9.6Hz, J=16.0Hz, CH*H*CO_2Me), 2.76 (dd, 1H, J=5.3Hz, J=16.0Hz, C*H*HCO_2Me), 2.17-2.08 (m, 1H, CHCH*H*CH_2), 1.73-1.68 (m, 1H, CHC*H*HCH_2), 1.29-1.22 (m, 2H, C*H*$_2$$CH_2$Si), 0.60-0.38 (m, 2H, CH_2Si), -0.09 (s, 9H, Si(CH_3)$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2 (OCO), 170 (NCO), 135.7 (CHPhth), 133.6 (CqPhth), 125 (CHPhth), 53.5 (CO_2*C*H$_3$), 49.4 (NCH), 38.5 (*C*H$_2$$CO_2$Me), 37.7 (CH*C*H$_2$), 26.9, 25.2 ($CH_2$SiMe$_3$), 22.5, 17.8 (*CH*$_2$$CH_2$SiMe$_3$), 0.021 (SiMe$_3$);

ν_{max}(CCl_4)/cm^{-1}: 1776, 1745, 1716, 1249, 1204;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{25}NO_4Si$: 347.1553 (347.1546).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-cyano-hexanoic acid methyl ester (3-26-3)



3-26-3

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and allyl cyanide (43 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 103 mg **3-26-3** (yield: 82%) as a pale yellow oil.

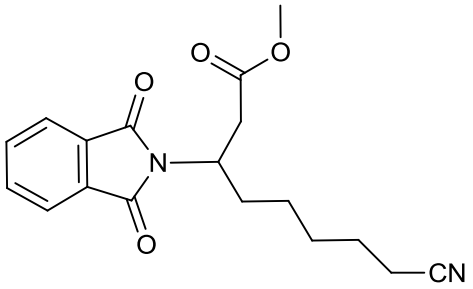
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.89-7.81 (m, 2H, CHPhth), 7.77-7.69 (m, 2H, CHPhth), 4.71-4.63 (1H, m, NCH), 3.62 (s, 3H, CO_2CH_3), 3.18 (dd, 1H, J=9.0Hz, J=16.3Hz, CH*H*CO_2Me), 2.84 (dd, 1H, J=5.7Hz, J=16.3Hz, C*H*HCO_2Me), 2.38 (t, 2H, J=7.2Hz, CH_2CN), 2.30-2.20 (m, 1H, CH*H*CH_2CN), 1.90-1.82 (m, 1H, C*H*HCH_2CN), 1.68-1.58 (m, 2H, CHC*H_2*);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.9 (OCO), 168.1 (NCO), 134.1 (CHPhth), 131.4 (CqPhth), 123.3 (CHPhth), 119 (CH_2*C*N), 51.8 (CO_2*C*H_3), 46.7 (NCH), 36.5 (*C*H_2CO_2Me), 31.1(CH*C*H_2), 22.2 (*C*H_2CH_2CN), 16.5 (*C*H_2CN);

IR (CCl_4): νmax 2248, 1776, 1745, 1716, 1211, 1172;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{16}N_2O_4$: 300.1110 (300.1100).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-8-cyano-octanoic acid methyl ester (3-26-4)



3-26-4

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and hex-5-enenitrile (61 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 3:1 v/v) afforded 112 mg **3-26-4** (yield: 81%) as a pale yellow oil.

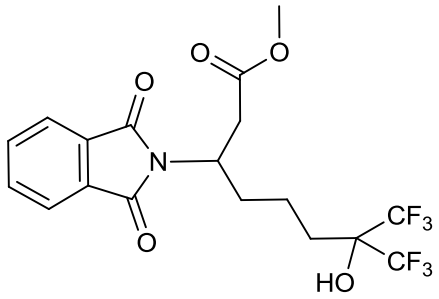
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.78 (m, 2H, CHPhth), 7.75-7.68 (m, 2H, CHPhth), 4.71-4.62 (1H, m, NCH), 3.61 (s, 3H, CO_2CH_3), 3.15 (dd, 1H, J=9.2Hz, J=16.1Hz, CH*H*CO_2Me), 2.80 (dd, 1H, J=5.6Hz, J=16.1Hz, C*H*HCO_2Me), 2.29 (t, 2H, J=7.1Hz, CH_2CN), 2.05-1.97 (m, 1H, C*H*HCH_2CN), 1.75-1.66 (m, 1H, CH*H*CH_2CN), 1.64-1.57 (m, 2H, CHC*H*$_2$), 1.51-1.43 (m, 2H, C*H*$_2CH_2CH_2CN$), 1.33-1.26 (m, 2H, $CHCH_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.1 (OCO), 168.1 (NCO), 133.8 (CHPhth), 131.5 (CqPhth), 123.14, 123.11 (CHPhth), 119.3 (CH_2*C*N), 51.602 (CO_2*C*H_3), 47.6 (NCH), 36.6 (*C*H_2CO_2Me), 31.7 (CH*C*H_2), 27.9 ($CHCH_2CH_2$*C*H_2), 25.3 (*C*H_2CH_2CN), 25 (*C*H_2CH_2CN), 16.8 (*C*H_2CN);

IR (CCl_4): νmax 2249, 1776, 1744, 1712, 1206, 1178;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{20}N_2O_4$: 328.1423 (328.1426).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-8,8,8-trifluoro-7-hydroxy-7-(trifluoromethyl)-octanoic acid methyl ester (3-26-5)



3-26-5

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and 1,1,1-Trifluoro-2-(trifluoromethyl)-pent-4-en-2-ol (133 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 106 mg **3-26-5** (yield: 57%) as a colorless oil.

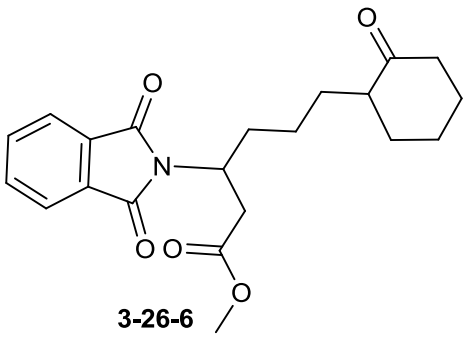
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.78 (m, 2H, CHPhth), 7.77-7.68 (m, 2H, CHPhth), 4.71-4.63 (1H, m, NCH), 3.71 (s, 1H, OH), 3.61 (s, 3H, CO_2CH_3), 3.17 (dd, 1H, J=8.9Hz, J=16.4Hz, CH*H*CO_2Me), 2.84 (dd, 1H, J=5.9Hz, J=16.4Hz, C*H*HCO_2Me), 2.25-2.17 (m, 1H, CH_2CH*H* $(CF_3)_2$), 2.09-2.02 (m, 1H, CH_2C*H*H$(CF_3)_2$), 1.87-1.76 (m, 2H, C*H*$_2CH_2(CF_3)_2$), 1.63-1.54 (m, 2H, CHC*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3 (OCO), 168.6 (NCO), 134.2 (CHPhth), 131.5 (CqPhth), 123 (q, 1H, J=271.1Hz, *C*F_3), 123.4 (CHPhth), 51.9 (CO_2*C*H_3), 47 (NCH), 36.6 (*C*H_2CO_2Me), 32.2 (CH*C*H_2), 29.324 (*C*H_2CH(OH)$(CF_3)_2$), 18.432 (CHCH_2*C*H_2);

IR (CCl_4): νmax 3474, 1776, 1744, 1717, 1206, 1178;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{17}F_6NO_5$: 441.1011 (441.101).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-(2-oxocyclohexyl)-hexanoic acid methyl ester (3-26-6)



3-26-6

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and 2-allylcyclohexanone (88 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 110 mg **3-26-6** (yield: 71%) as a colorless oil and a mixture of two diastereoisomers in a ratio 1:1.

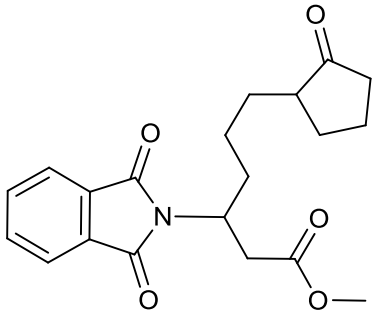
^{1}H NMR (400 MHz; $CDCl_3$): *Mixture of diastereoisomer :* δ_H 7.85-7.76 (m, 2H, CHPhth), 7.76-7.68 (m, 2H, CHPhth), 4.69-4.61 (1H, m, NCH), 3.60 (s, 3H, CO_2CH_3), 3.21-3.13 (m, 1H, J=9.5Hz, J=16.1Hz, CH*H*CO_2Me), 2.81-2.72(m, 1H, J=5.0Hz, J=16.0Hz, C*H*HCO_2Me), 2.36-2.28 (m, 1H, C*H*$COCH_2$), 2.26-2.17 (m, 2H, COC *H*$_2CH_2$), 2.09-1.95 (m, 3H, $COCH_2CH$, $COCH_2CH_2CH$, $CHCH_2$), 1.71-1.67 (m, 3H, $COCH_2CH$*H*, $COCH_2CH_2CH$*H*, CHCH*H*), 1.66-1.56 (m, 3H, COCH*C*H*H*, CHC*H*$_2CH_2$), 1.39-1.28 (m, 3H, COCH*CH*H, $CHCH_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): *Mixture of diastereoisomer :* δ_C 212.9 (CH*C*O), 171.4, 171.3 (O*C*O), 168.3 (NCO), 133.9 (CHPhth), 131.8 (CqPhth), 123.2 (CHPhth), 51.7 (CO_2CH_3), 50.5 (NCH), 47.97, 47.92 (*C*HCO), 41.9 ($COCH_2$), 36.7 (CH_2CO_2Me), 34, 33.8 ($COCHCH_2$), 32.5 ($NCHCH_2$), 28.9, 28.8 ($COCH_2CH_2$), 27.9 ($COCHCH_2$), 24.9 ($COCH_2CH_2CH_2$), 23.9 ($CHCH_2CH_2CH_2CH$);

IR (CCl_4): νmax 1776, 1745, 1715, 1208, 1173;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{25}NO_5$: 371.1733 (371.1743).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-(2-oxocyclopentyl)-hexanoic acid methyl ester (3-26-7)



3-26-7

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and 2-Allyl-cyclopentanone (79 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 91 mg **3-26-7** (yield: 61%) as a colorless oil and a mixture of two diastereoisomers in a ratio 1:1.

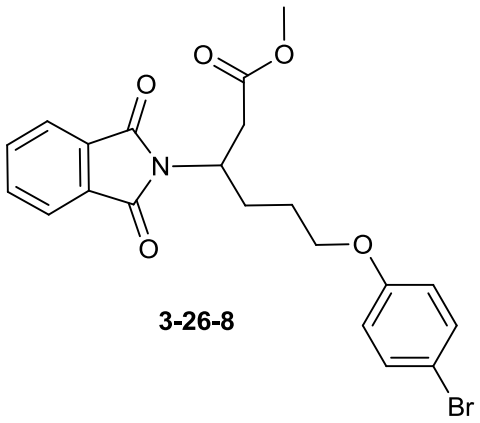
^{1}H NMR (400 MHz; $CDCl_3$): *Mixture of diastereoisomer :* δ_H 7.89-7.77 (m, 2H, CHPhth), 7.76-7.65 (m, 2H, CHPhth), 4.70-4.61 (1H, m, NCH), 3.60 (s, 3H, CO_2CH_3), 3.17 (dd, 0.5 H, J=2.1Hz, J=9.5Hz, CH*H*CO_2Me), 3.13 (dd, 0.5 H, J=2.1Hz, J=9.5Hz, CH*H*CO_2Me), 2.79 (dd, 0.5 H, J=1.1Hz, J=5.3Hz, C*H*HCO_2Me), 2.75 (dd, 0.5 H, J=1.0Hz, J=5.3Hz, C*H*HCO_2Me), 2.30-2.21 (m, 1H, C*H*$COCH_2$), 2.16-2.07 (m, 3H, COC*H*HCH_2, $COCH_2$C*H*H, $COCH_2CH_2$C*H*H), 2.01-1.92 (m, 2H, COCH*H*, $COCH_2$CH*H*), 1.77-1.69 (m, 3H, $COCH_2CH_2$C*H*H, NCHCH_2), 1.48-1.41 (m, 1H, COCHC*H*H), 1.34-1.21 (m, 3H, COCHCH*H*, $NCHCH_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): *Mixture of diastereoisomer :* δ_C 171.4, 168.3 (NCO), 134 (CHPhth), 131.8 (CqPhth), 123.3 (CHPhth), 51.8 (CO_2CH_3), 48.9, 48.9 (NCH), 48, 47.9 (*C*HCO), 38.1 (*C*H_2CO_2Me), 36.8, 36.7 ($COCH_2$), 32.4, 32.3, 29.6, 29.6, 29.2, 29.1, 24.5, 24.4, 20.7 (CH_2);

IR (CCl_4): νmax 1776, 1743, 1716, 1206, 1173;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{23}NO_5$: 357.1576 (357.1575).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-(4-bromophenoxy)-hexanoic acid meth-yl ester (3-26-8)



3-26-8

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and 1-(allyloxy)-4-bromobenzene (136 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 119 mg **3-26-8** (yield: 64%) as a yellow oil.

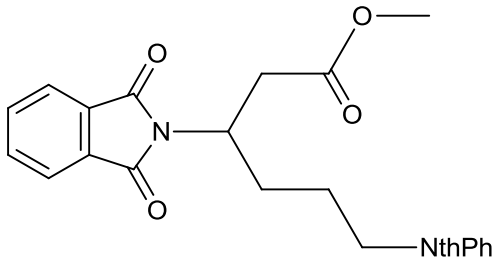
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.78 (m, 2H, CHPhth), 7.75-7.66 (m, 2H, CHPhth), 7.34 (d, 2H, J=8.9Hz, Ar), 6.80 (d, 2H, J=8.9Hz, Ar), 4.75-4.68 (1H, m, NCH), 3.90 (dt, 2H, J=1.6Hz, J=6.4Hz, C*H*$_2$OPhBr), 3.60 (s, 3H, CO_2CH_3), 3.21 (dd, 1H, J=9.5Hz, J=16.1Hz, CH*H*CO_2Me), 2.82 (dd, 1H, J=5.3Hz, J=16.1Hz, C*H*HCO_2Me), 2.29-2.21 (m, 1H, NCHCH_2C*H*H), 1.97-1.89 (m, 1H, NCHCH_2CH*H*), 1.76-1.68 (m, 2H, NCHC*H*$_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.2 (C=O), 168.3, (C=O), 158.8 (Cq-O), 134.0, 133.9 (CPhth), 131.7 (CqPhth), 129.3 (Ar), 123.3, 123.2 (CPhth), 120.6 (Ar), 114.4 (Ar), 66.7 (*C*H_2OPh), 51.8 (CO_2CH_3), 47.7 (NCH), 36.7 (*C*H_2CO_2), 28.9 (NCH*C*H_2), 24.3 (*C*H_2CH_2OPh);

IR (CCl_4): νmax 1776, 1745, 1716, 1241, 1173, 1047;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{20}BrNO_5$: 445.0525 (445.0534).

3,6-bis(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)hexanoic acid methyl ester (3-26-9)



3-26-9

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and 2-allylisoindoline-1,3-dione (119 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 116 mg **3-26-9** (yield: 66%) as a colorless oil.

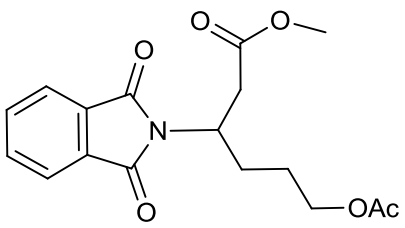
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.84-7.75 (m, 4H, CHPhth), 7.75-7.64 (m, 4H, CHPhth), 4.73-4.64 (m, 1H, NCH), 3.67 (m, 2H, NCH_2), 3.58 (s, 3H, CO_2CH_3), 3.18 (dd, 1H, J=9.6Hz, J=16.1Hz, CH*H*CO_2Me), 2.77 (dd, 1H, J=5.3Hz, J=16.1Hz, C*H*HCO_2Me), 2.19-2.09 (m, 1H, NCH_2C*H*H), 1.81-1.73 (m, 1H, NCH_2CH*H*), 1.69-1.61 (m, 2H, NCHCH_2CH_2);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.1 (OCO), 168.2, 168.2(NCO), 133.9, 133.9 (CHPhth), 132, 131.7 (CqPhth), 123.3, 123.2 (CHPhth), 51.8 (CO_2CH_3), 47.5 (N*C*H), 37.3 (NCH_2), 36.6 (CH_2CO_2Me), 29.6 (NCHCH_2), 25.5 (NCH_2CH_2);

IR (CCl_4): νmax 1776, 1745, 1718, 1206, 1173;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{20}N_2O_6$: 420.1321 (420.1322).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-acetoxy-hexanoic acid methyl ester (3-26-10)



3-26-10

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and allyl acetate (64 mg 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1~4:1 v/v) afforded 99 mg **3-26-10** (yield: 71%) as a colorless oil.

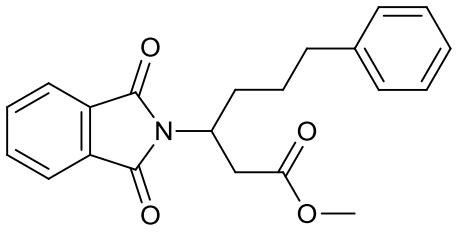
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.79 (m, 2H, CHPhth), 7.76-7.67 (m, 2H, CHPhth), 4.71-4.63 (1H, m, NCH), 4.04 (t, 2H, J=6.5Hz, C*H*$_2$OAc), 3.60 (s, 3H, CO_2CH_3), 3.18 (dd, 1H, J=9.4Hz, J=16.1Hz, CH*H*CO_2Me), 2.80 (dd, 1H, J=5.4Hz, J=16.1Hz, C*H*HCO_2Me), 2.01(s, 3H, OCOC*H*$_3$), 1.87-1.76 (m, 2H, NCHC*H*$_2$), 1.63-1.55 (m, 2H, NCHCH_2C*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.2 (OCO), 171 (OCO), 168.2 (NCO), 134 (CHPhth), 131.7 (CqPhth), 123.3 (CHPhth), 63.6 (CH_2*C*H$_2$OAc), 51.8 (CO_2*C*H$_3$), 47.7 (NCH), 36.7 (*C*H$_2$$CO_2$Me), 28.9 (NCH*C*H$_2$), 25.5 (NCHC$H_2$*C*H$_2$);

ν_{max}(CCl_4)/cm^{-1}: 1777, 1744, 1717, 1237, 1173;

HRMS (EI+): *m/z* calculated (found) for $C_{17}H_{19}NO_6$: 333.1212 (333.1210).

3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-6-phenyl-hexanoic acid methyl ester (3-26-11)



3-26-11

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-25** (150 mg, 0.42 mmol) and allylbenzene (76 mg, 0.64 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1~5:1 v/v) afforded 112 mg **3-26-11** (yield: 76%) as a colorless oil.

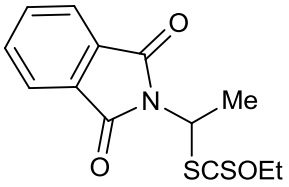
^{1}H NMR (400 MHz; $CDCl_3$): δ_H -7.85-7.79 (m, 2H, CHPhth), -7.75-7.66 (m, 2H, CHPhth), 7.23 (t, 2H, J=7.3Hz, Ar), 7.15 (t, 1H, Ar), 7.12 (d, 2H, J=6.9Hz, Ar), 4.74-4.66 (m, 1H, NCH), 3.6 (s, 3H, CO_2CH_3), 3.17 (dd, 1H, J=9.5Hz, J=16.1Hz, CH*H*CO_2Me), 2.77 (dd, 1H, J=5.3Hz, J=16.1Hz, C*H*HCO_2Me), 2.66-2.58 (m, 2H, CH_2Ph), 2.19-2.11 (m, 1H, CH*H*CH_2Ph), 1.82-1.73 (m, 1H, C*H*HCH_2Ph), 1.64-1.57 (m, 2H, NCHC*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3 (OCO), 168.3 (NCO), 141.7 (CqAr), 133.9 (CHPhth), 131.7 (CqPhth), 128.3, 128.2, 125.8 (Ar), 123.2 (CHPhth), 51.7 (CO_2CH_3), 47.8 (NCH), 36.7 (*C*H$_2$CO$_2$Me), 35.2 (ArCH$_2$), 31.8 (NCH*C*H$_2$), 28.1 (ArCH$_2$*CH$_2$*);

ν_{max}(CCl_4)/cm^{-1}: 1776, 1745, 1716, 1206, 1173;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{21}NO_4$: 351.1471 (351.1471).

Dithiocarbonic acid [1-bis-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1-ethyl] ester *O*-ethyl ester (3-27)



3-27

To a solution of **SM-1** (4 g, 23 mmol) in CCl_4 (150 ml) NBS (4.8g, 27 mmol) was added and then the solution was heated at reflux under nitrogen for 2h; the reaction was initiated by irradiation with a 300 W lamp. The reaction mixture was then cooled, filtered and washed with sodium thiosulfate. After extracting the solution with DCM, the organic layer was concentrated under reduced pressure to obtain 4.9 g **SM-2** (yield: 85%) without further purification. **SM-2** (4.9 g, 20 mmol) was dissolved in acetone (2 ml per mmol). KSCSOEt (3.5 g, 22 mmol) was then added portion wise over a period of five minutes. It was then left to stir for further twenty minutes before the acetone was evaporated off under reduced pressure. The residue was then taken up in DCM/H_2O and extracted. The DCM layers were dried over Na_2SO_4 before being filtered and evaporated under reduced pressure to yield the crude xanthate. This was then purified by column chromatography using petroleum ether: ethyl acetate, 10:1~4:1 v/v, to obtain 4.8 g **3-27** (yield: 81%) as a pale yellow solid which was crystallized from ethyl acetate/ petroleum ether.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.85-7.76 (m, 2H, CHPhth), 7.77-7.69 (m, 2H, CHPhth), 6.34 (q, 1H, J=7.3Hz, CHS), 4.60 (q, 2H, OCH_2CH_3), 1.82 (d, 3H, J=7.3Hz), 1.37 (t, 3H, J=7.1Hz, OCH_2CH_3);

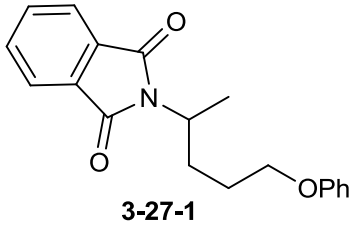
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 211.1 (C=S), 166.6 (C=O), 134.4 (CPhth), 131.7 (CPhth), 123.6 (CPhth), 70.3 (OCH_2CH_3), 53.4 (CHS), 20 ($CHSCH_3$), 13.8 (OCH_2CH_3);

IR (CCl_4): ν max 2928, 1781, 1723, 1376, 1223, 1044;

HRMS (EI+): *m/z* calculated (found) for $C_{13}H_{13}NO_3S_2$: 295.0337 (295.0346); MP:

103~104 ℃.

2-(5-Phenoxypentan-2-yl)isoindoline-1,3-dione (3-27-1)



3-27-1

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-27** (100 mg, 0.34 mmol) and allyl phenyl ether (68 mg, 0.51 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 81 mg **3-27-1** (yield: 78%) as a colorless solid.

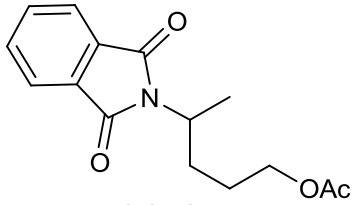
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.89-7.78 (m, 2H, CHPhth), 7.74-7.63 (m, 2H, CHPhth), 7.24 (s, 2H, Ar), 6.91 (t, 1H, J=6.7Hz, Ar), 6.86 (d, 2H, J=7.8Hz, Ar), 4.50-4.41 (m, 1H, NCH), 3.95 (dt, 2H, J=1.6Hz, J=6.4Hz, CH_2OPh), 2.31-2.20 (m, 1H,CH*H*CH_2OPh), 1.99-1.92 (m, 1H, C*H*HCH_2OPh), 1.82-1.74- (m, 2H, $NCHCH_2$), 1.52 (d, 3H, J=6.9Hz, $NCHCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.4 (C=O), 158.8 (Ar), 133.8 (CPhth), 131.8 (CqPhth), 129.3 (Ar), 123 (CPhth), 120.5 (Ar), 114.3 (Ar), 67 (CH_3OPh), 47.1 (NCH), 30.1 (NCH*C*H_2), 26.5 ($NCHCH_2$*C*H_2), 18.7 (NCH*C*H_3);

IR (CCl_4): νmax 2939, 1713, 1775, 1470, 1369, 1172, 1051;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{19}NO_3$: 309.1365 (309.1372), MP: 97 ℃.

4-(1,3-Dioxoisoindolin-2-yl)pentyl acetate (3-27-2)



3-27-2

Following the general procedure A for radical addition, the reaction was carried out

with a solution of **3-27** (100 mg, 0.34 mmol) and allyl acetate (51 mg, 0.51 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 66 mg **3-27-2** (yield: 71%) as a colorless oil.

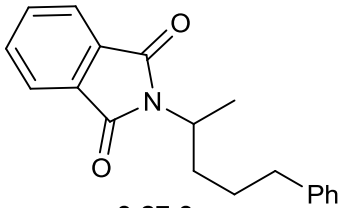
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.82-7.72 (m, 2H, CHPhth), 7.72-7.63 (m, 2H, CHPhth), 4.48-4.41 (m, 1H, NCH), 4.03 (t, 2H, J=6.5Hz, CH_2OAc), 2.15-2.08 (m, 1H, CH*H*CH_2OAc), 2.00 (s, 3H, $OCOCH_3$), 1.84-1.76 (m, 1H, C*H*HCH_2OAc), 1.63-1.54 (m, 2H, $NCHCH_2$), 1.47 (d, 3H, J=6.9Hz, $NCHCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_c 171 (CH_3CO), 168.4 (C=O), 133.9 (CPhth), 131.9 (CqPhth), 123.1 (CPhth), 63.9 (CH_2OAc), 47.1 (NCH), 30.2 ($NCHCH_2$), 25.9 ($NCHCH_2CH_2$), 20.9 (CH_3CO), 18.7 ($NCHCH_3$);

IR (CCl_4): νmax 2928, 1742, 1713, 1469, 1368, 1239, 1052;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{17}NO_4$: 275.1158 (275.1151).

2-(5-Phenylpentan-2-yl)isoindoline-1,3-dione (3-27-3)



3-27-3

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-27** (100 mg, 0.34 mmol) and allylbenzene (60 mg, 0.51 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 75 mg **3-27-3** (yield: 76%) as a colorless oil.

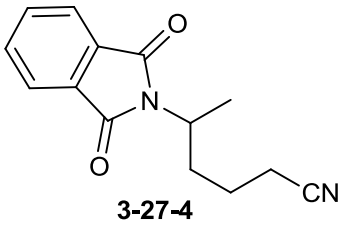
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.86-7.77 (m, 2H, CHPhth), 7.74-7.66 (m, 2H, CHPhth), 7.29-7.21 (m, 2H, Ar), 7.16 (t, 1H, J=6.7Hz, Ar), 7.15 (d, 2H, J=7.8Hz, Ar), 4.43-4.37 (m, 1H, NCH), 2.69-2.56 (m, 2H, CH_2Ph), 2.17-2.12 (m, 1H, CH*H*CH_2Ph), 1.82-1.75 (m, 1H, C*H*HCH_2Ph), 1.64-1.55 (m, 2H), 1.52 (d, 3H, J=6.9Hz, $NCHCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.4 (C=O), 133.7 (CPhth), 131.9 (CqPhth), 141.961, 128.288, 128.207, 125.686 (Ar), 123 (CPhth), 47.1 (NCH), 35.4 (CH_2Ph), 33.2 (NCH*C*H_2), 28.6 (NCHCH$_2$*C*H_2), 18.649 (NCH*C*H_3);

IR (CCl_4): νmax 2937, 1713, 1775, 1468, 1378, 1141, 1037;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{19}NO_2$: 293.1416 (293.1416).

5-(1,3-Dioxoisoindolin-2-yl)hexanenitrile (3-27-4)



3-27-4

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-27** (100 mg, 0.34 mmol) and allyl cyanide (35 mg, 0.51 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 67 mg product **3-27-4** (yield: 82%) as a pale yellow oil.

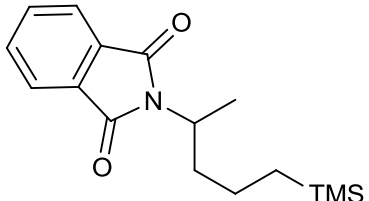
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.81-7.72 (m, 2H, CHPhth), 7.71-7.63 (m, 2H, CHPhth), 4.37-4.29 (m, 1H, NCH), 2.33 (t, 2H, J=7.2Hz, CH_2CN), 2.25-2.17 (m, 1H, CH*H*CH_2CN), 1.89-1.81 (m, 1H, C*H*HCH_2CN), 1.62-1.54 (m, 2H, NCHCH_2), 1.46 (d, 3H, J=7.2Hz, NCHCH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.3 (C=O), 134 (CPhth), 131.7 (CqPhth), 123.1 (CPhth), 119.162 (CN), 46.3 (NCH), 32.5 (NCH*C*H_2), 22.7 (NCHCH$_2$*C*H_2), 18.6 (NCH*C*H_3), 16.688 (*C*H_2CN);

IR (CCl_4): νmax 2929, 1713, 1776, 1469, 1370, 1144, 1041;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{14}N_2O_2$: 242.1055 (242.1057).

2-(5-(Trimethylsilyl)pentan-2-yl)isoindoline-1,3-dione (3-27-5)



3-27-5

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-27** (100 mg, 0.34 mmol) and allyl trimethylsilane (78 mg, 0.68 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 64 mg **3-27-5** (yield: 66%) as a colorless oil.

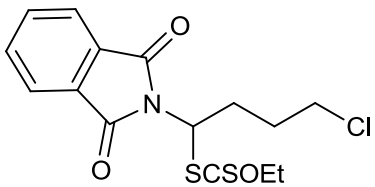
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.86-7.77 (m, 2H, CHPhth), 7.74-7.66 (m, 2H, CHPhth), 4.42-4.33 (m, 1H, NCH), 2.11-2.03 (m, 1H, CH*H*CH_2TMS), 1.81-1.72 (m, 1H, C*H*HCH_2TMS), 1.67-1.59 (m, 2H NCHCH_2) 1.45 (d, 3H, J=6.9Hz), 0.55-0.44 (m, 2H, CH_2TMS), -0.08 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ_c 168.5 (C=O), 133.7 (CPhth), 132 (CqPhth), 123 (CPhth), 46.9 (NCH), 37.3 (NCH*C*H_2), 21.1 (NCHCH_2*C*H_2), 18.6 (NCH*C*H_3), 16.1 (CH_2TMS), -1.8 (TMS);

IR (CCl_4): νmax 2927, 1712, 1774, 1378, 1248, 1108, 1025;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{23}NO_2Si$: 289.1498 (289.1504).

4-Chloro-1-(1,3-dioxoisoindolin-2-yl)butyl-O-ethyl carbonodithioate (3-30)



3-30

To a solution of **SM-1** (4.25 g, 18 mmol) in CCl_4 (150 ml), NBS (3.2g, 18 mmol) was added and then the solution was heated at reflux under nitrogen for 4h, meanwhile the reaction was initiated by irradiation with a 300 W lamp. The reaction mixture was

then cooled, filtered and washed with sodium thiosulfate. After extracting the solution with DCM, the organic layer was concentrated under reduced pressure to obtain 5 g **SM-3** (yield: 88%) without further purification. **SM-3** (5 g, 15.8 mmol), was dissolved in acetone (2 ml per mmol). KSCSOEt (2.4 g, 15 mmol) was added portion wise over a period of five minutes. It was then left to stir until the starting material was totally consumed by monitoring TLC. After concentrated the resulting solution the residue was then taken up in DCM/H_2O and extracted 3 times. The DCM layers were dried over Na_2SO_4 before being filtered and evaporated under reduced pressure to yield the crude xanthate. This was then purified by column chromatography using petroleum ether: ethyl acetate, 10:1~4:1 v/v, to obtain 4.8 g **3-30** (yield: 86%) as a pale yellow sticky liquid which was crystallized from ethyl acetate/ petroleum ether.

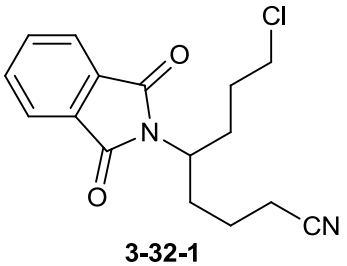
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.79 (m, 2H, CHPhth), 7.79-7.69 (m, 2H, CHPhth), 6.24 (dd, 1H, J=7.0Hz, J=9.1Hz, CHS), 4.60 (q, 2H, J=7.1Hz, OC*H*$_2$$CH_3$), 3.54 (t, 2H, J=6.5Hz, *CH*$_2$Cl), 2.39-2.29 (m, 2H, CHS*CH*$_2$) , 1.92-1.81 (m, 2H, *CH*$_2$$CH_2$Cl), 1.38 (t, 3H, J=7.1Hz, OCH_2C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 210.17 (C=S), 166.6 (C=O), 134.3 (CPhth), 131.3 (CPhth), 123.5 (CPhth), 70.4 (O*C*$H_2$$CH_3$), 56.8 (*C*HS), 43.5 (*C*H_2Cl), 30.6 (CHS*C*H_2), 29.3 (*C*$H_2$$CH_2$Cl), 13.6($OCH_2$*C*$H_3$);

IR (CCl_4): νmax 2934, 1767, 1731, 1386, 1232, 1076;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{16}ClNO_3S_2$: 357.0260 (357.0266); MP: 132~133 ℃.

8-Chloro-5-(1,3-dioxoisoindolin-2-yl)octanenitrile (3-32-1)



3-32-1

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-30** (100 mg, 0.28 mmol) and allyl cyanide (40 mg, 0.33 mmol),

and needed 30 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 54 mg **3-32-1** (yield: 64%) as a pale yellow oil.

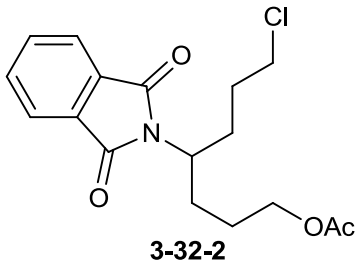
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.79 (m, 2H, CHPhth), 7.79-7.70 (m, 2H, CHPhth), 4.27-4.18 (1H, m, NCH), 3.59-3.48 (m, 2H, *CH_2*Cl), 2.36 (t, 2H, J=7.2Hz, C*H_2*CN), 2.31-2.23 (m, 2H, NCHC*H*H, NCHCH*H*), 1.98-1.83 (m, 2H, NCHCH*H*, NCHC*H*H), 1.77-1.68 (m, 2H, *CH_2*CH_2Cl), 1.67-1.57 (m, 2H, NCHCH_2C*H_2*);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.5 (NCO), 134.2 (CHPhth), 131.4 (CqPhth), 123.4 (CHPhth), 119.1 (*C*N), 50.2 (N*C*H), 44.1(*C*H_2Cl), 31.3 (NCH*C*H_2), 29.5 (NCH*C*H_2), 29.4 (*CH_2*CH_2Cl), 22.5 (*C*$H_2$$CH_2$CN), 16.7 (*C*$H_2$CN);

IR (CCl_4): νmax 2938, 1771, 1733, 1389, 1236, 1078;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{17}ClN_2O_2$: 304.0979 (304.0985).

7-Chloro-4-(1,3-dioxoisoindolin-2-yl)heptyl acetate (3-32-2)



3-32-2

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-30** (100 mg, 0.28 mmol) and allyl acetate (56 mg 0.56 mmol), and needed 30 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1~4:1 v/v) afforded 94 mg **3-32-2** (yield: 68%) as a colorless oil.

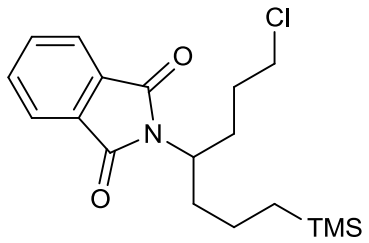
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.86-7.77 (m, 2H, CHPhth), 7.77-7.66 (m, 2H, CHPhth), 4.28-4.19 (1H, m, NCH), 4.04 (t, 2H, J=6.5Hz, C*H_2*OAc), 3.56-3.47 (m, 2H, *CH_2*Cl), 2.26-2.17 (m, 2H, NCHC*H_2*), 2.01 (s, 3H, OAc), 1.96-1.87 (m, 1H, NCHC*H*H), 1.85-1.78 (m, 1H, NCHCH*H*), 1.76-1.65 (m, 2H, *CH_2*CH_2Cl), 1.28-1.19 (m, 2H, NCHCH_2C*H_2*);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171 (O*C*OCH_3), 168.6 (NCO), 134 (CHPhth),

131.5 (CqPhth), 123.3 (CHPhth), 63.8 (*C*H_2OAc) 50.9 (N*C*H), 44.2 (*C*H_2Cl), 29.6 (NCH*C*H_2), 29.5 (NCH*C*H_2), 28.9 (*CH*$_2$$CH_2$Cl), 25.8 (*C*$H_2$$CH_2$OAc), 20.1 (O*C*$H_3$); **$\nu_{max}$($CCl_4$)/$cm^{-1}$**: 2989, 1712, 1766, 1389, 1268, 1046;

HRMS (EI+): *m/z* calculated (found) for $C_{17}H_{20}ClNO_4$: 337.1081 (337.1087).

2-(1-Chloro-7-(trimethylsilyl)heptan-4-yl)isoindoline-1,3-dione (3-32-3)



3-32-3

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-30** (100 mg, 0.28 mmol) and allyl trimethylsilane (96 mg, 0.84 mmol), and needed 30 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 96 mg **3-32-3** (yield: 61%) as a colorless oil.

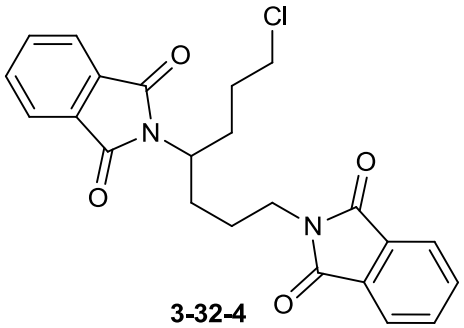
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.79 (m, 2H, CHPhth), 7.78-7.67 (m, 2H, CHPhth), 4.28-4.19 (1H, m, NCH), 3.57-3.47 (m, 2H, *CH*$_2$Cl), 2.22-2.11 (m, 2H, NCHC*H*$_2$), 1.92-1.83 (m, 1H, NCHCH*H*), 1.77-1.69 (m, 3H, NCHC*H*H, *CH*$_2$$CH_2$Cl), 1.31-1.20 (m, 2H, NCHCH_2C*H*$_2$), 0.53-0.42 (m, 2H, C*H*$_2$TMS), -0.09 (s, 9H, TMS);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.7 (NCO), 134 (CHPhth), 131.7 (CqPhth), 123.1 (CHPhth), 50.9 (N*C*H), 44.4 (*C*H_2Cl), 36 (NCH*C*H_2), 29.7 (NCH*C*H_2), 29.6 (*C*$H_2$$CH_2$Cl), 20.9 (*C*$H_2$$CH_2$TMS), 16.093 (*C*$H_2$TMS), -1.8 (TMS);

IR (CCl_4): νmax 2934, 1756, 1346, 1287, 1023;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{26}ClNO_2Si$: 351.1421 (351.1416).

2,2'-(7-Chloroheptane-1,4-diyl)bis(isoindoline-1,3-dione) (3-32-4)



3-32-4

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-30** (100 mg, 0.28 mmol) and 2-allylisoindoline-1,3-dione (104 mg, 0.56 mmol), and needed 35 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 116 mg **3-32-4** (yield: 64%) as a colorless oil.

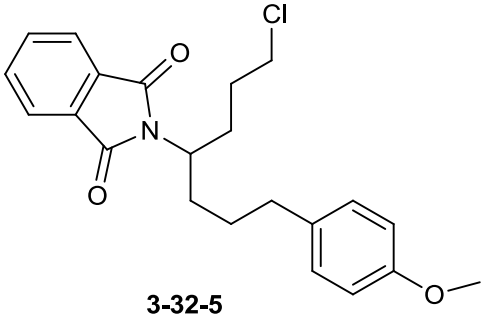
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.85-7.76 (m, 4H, CHPhth), 7.75-7.64 (m, 4H, CHPhth), 4.30-4.21 (1H, m, NCH), 3.71-3.62 (m, 2H, N*C*H_2), 3.5 (t, 2H, J=6.3Hz, *C*H_2Cl), 2.27-2.16 (m, 2H, NCHC*H*$_2$), 1.92-1.84 (m, 1H, NCHCH*H*), 1.77-1.65 (m, 5H, NCHC*H*H, *C*H_2CH_2Cl, NCHCH_2C*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.5, 168.3 (NCO), 134, 133.9 (CHPhth), 132, 131.6 (CqPhth), 123.3, 123.2 (CHPhth), 50.8 (N*C*H), 44.2 (*C*H_2Cl), 37.3 (N*C*H_2), 29.6 (NCH*C*H_2), 29.5 (NCH*C*H_2), 29.5 (*C*H_2CH_2Cl), 25.7 (*C*H_2NCH_2);

IR (CCl_4): νmax 2937, 1718, 1773, 1356, 1244, 1038;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{21}ClN_2O_4$: 424.1190 (424.1198).

2-(1-Chloro-7-(4-methoxyphenyl)heptan-4-yl)isoindoline-1,3-dione (3-32-5)



3-32-5

Following the general procedure A for radical addition, the reaction was carried out

with a solution of **3-30** (100 mg, 0.28 mmol) and allyl phenyl ether (75 mg, 0.56 mmol), and needed 40 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 10:1 v/v) afforded 72 mg **3-32-5** (yield: 67%) as a pale yellow oil.

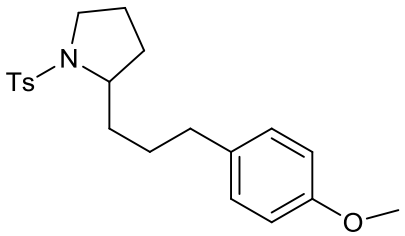
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.76 (m, 2H, CHPhth), 7.75-7.68 (m, 2H, CHPhth), 7.03 (d, 2H, J=8.6Hz, Ar), 6.78 (d, 2H, J=8.6Hz, Ar), 4.31-4.22 (1H, m, NC*H*), 3.76 (s, 3H, ArOCH_3), 3.55-3.46 (m, 2H, CH_2Cl), 2.60-2.49 (m, 2H, CH_2Ar), 2.22-2.13 (m, 2H, NCHCH_2), 1.93-1.82 (m, 1H, NCHCH*H*), 1.78-1.63 (m, 3H, NCHC*H*H, CH_2CH_2Cl,), 1.59-1.50 (m, 2H, $NCHCH_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): 168.7 (NCO), 157.8 (Ar), 134.03 (CHPhth), 134 (Ar), 131.7 (CqPhth), 129.3 (Ar), 123.3 (CHPhth), 113.8 (Ar), 55.3 (ArOCH_3), 51.2 (N*C*H), 44.4 (CH_2Cl), 34.5 (CH_2Ar), 31.9 (NCHCH_2), 29.7 (NCHCH_2), 28.7 (CH_2CH_2Cl), 25.2 (CH_2CH_2Ar);

IR (CCl_4): νmax 2946, 1778, 1723, 1343, 1223, 1067;

HRMS (EI+): *m/z* calculated (found) for $C_{22}H_{24}ClNO_3$: 385.1445 (385.1442).

2-(3-(4-Methoxyphenyl)propyl)-1-tosylpyrrolidine (3-33)



3-33

To a solution of **3-32-5** (72 mg, 0.18 mmol) in methanol (0.5 ml) was added 0.9 ml hydrazine in methanol (1M). The reaction was heated to reflux for 1h. Then the resulting solution was filtrated and the filtrate was concentrated under reduced pressure to get the residue. Without further purification, the residue was dissolved in 0.5 ml DCM and then 4-toluenesulfonyl chloride (35 mg, 0.18 mmol) and triethylamine (18 mg, 0.18 mmol) were added into the solution, which was stirred at room temperature for 8h. Finally, the solution was concentrated under reduced

pressure to obtain the residue which was then purified by column chromatography using petroleum ether: ethyl acetate, 10:1~4:1 v/v, to afford 48 mg **3-33** (yield: 71%) as a pale yellow stick liquid.

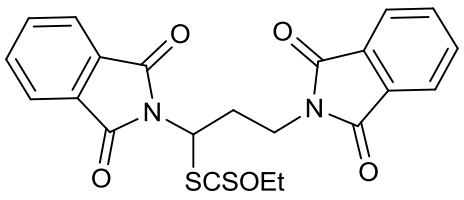
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.70 (d, 2H, J=8.2Hz, Ts), 7.29 (d, 2H, J=8.2Hz, Ts), 7.10 (d, 2H, J=8.1Hz, Ar), 6.83 (d, 2H, J=8.6Hz, Ar), 3.79 (s, 3H, ArOC*H*$_3$), 3.69-3.58 (m, 1H, NC*H*), 3.39-3.30 (m, 1H, NC*H*H), 3.24-3.16 (m, 1H, NCH*H*), 2.61-2.53 (m, 2H, ArC*H*$_2$), 2.42 (s, 3H, ArC*H*$_3$), 1.89-1.79 (m, 1H, NCH_2C*H*H), 1.79-1.68 (m, 1H, NCH_2CH*H*), 1.67-1.56 (m, 3H, NCHC*H*H, $CHCH_2C$*H*$_2$), 1.57-1.45 (m, 3H, NCHCH*H*, CHC*H*$_2CH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.7 (Ar), 143.1 (Ts), 135 (Ts), 134.5 (Ar), 129.6 (Ar), 129.2 (Ts), 127.4 (Ts), 113.7 (Ar), 60.4 (OCH_3), 55.2 (NCH_2), 48.8 (NCH), 36.1 (CH_2Ar), 34.9 ($CHCH_2$), 30.7 ($CHCH_2$), 28.3 (CH_2CH_2Ar), 24.1(NCH_2CH_2), 21.5 ($ArCH_3$);

IR (CCl_4): νmax 2986, 1778, 1722, 1333, 1287, 1054;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{27}NO_3S$: 373.1712 (373.1717).

Dithiocarbonic acid [1,3-bis-(1,3-dioxo-1,3-dihydroisoindol-2-yl)] ester ethyl ester (3-34)



3-34

To a solution of **3-5** (3 g, 9.00 mmol) in CCl_4 (150 ml), NBS (1.92g, 10.08 mmol) was added, then the solution was heated at reflux under nitrogen for 3 h; the reaction was initiated by irradiation with a 300 W lamp. The reaction mixture was then cooled, filtered and washed with sodium thiosulfate. After extracting the solution with DCM, the organic layer was concentrated under reduced pressure to yield 3.2 g **3-6** (86%) without further purification. **3-6** (3.2 g, 7.7 mmol) was dissolved in acetone (2 ml per mmol). Under nitrogen protection KSCSOEt (1.36 g, 8.5 mmol) was added portion

wise over a period of five minutes. It was then left to stir for further twenty minutes before the acetone was evaporated off under reduced pressure. The residue was then taken up in DCM/H_2O and extracted. The DCM layers were dried over Na_2SO_4 before being filtered and evaporated under reduced pressure to yield the crude xanthate. This was then purified by column chromatography using petroleum ether: ethyl acetate, 10:1~2:1 v/v to obtain 2.9 g **3-34** (83%) as a white solid which was crystallized from ethyl acetate/ petroleum ether.

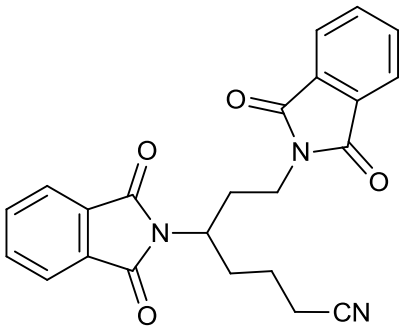
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.88-7.79 (m, 2H, CHPhth), 7.85-7.76 (m, 2H, CHPhth), 7.78-7.69 (m, 2H, CHPhth), 7.75-7.64 (m, 2H, CHPhth), 6.31-6.22 (m, 1H,CHS) 4.61 (q, 2H, J=7.1Hz, $COCH_2CH_3$), 3.84-3.75 (m, 2H, NCH_2), 2.77-2.68 (m, 2H, $CHSCH_2$), 1.36 (t, 3H, J=7.1Hz, $COCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 210.2 (C=S), 168 (C=O), 166.6 (C=O), 134.3, 134 (CPhth), 131.8, 131.5 (CqPhth), 123.6, 123.2 (CPhth), 70.4 (OCH_2CH_3), 54.9 (CHS), 35 ($CHSCH_2$), 31.4 (NCH_2), 13.6 (OCH_2CH_3);

IR (CCl_4): νmax 2983, 1777, 1724, 1542, 1394, 1228, 1112, 1049;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{13}N_2O_4$ [M-SCSOEt]: 333.0875 (333.0868); MP: 143~144 ℃.

5,7-bis-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-heptanenitrile (3-35-1)



3-35-1

Following the general procedure A for radical addition, the reaction was carried out with a solution of Xanthate **3-34** (100 mg, 0.22 mmol) and allyl cyanide (23 mg, 0.33 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum

ether: ethyl acetate, 2:1 v/v) afforded 62 mg **3-35-1** (yield: 71%) as a pale yellow oil.

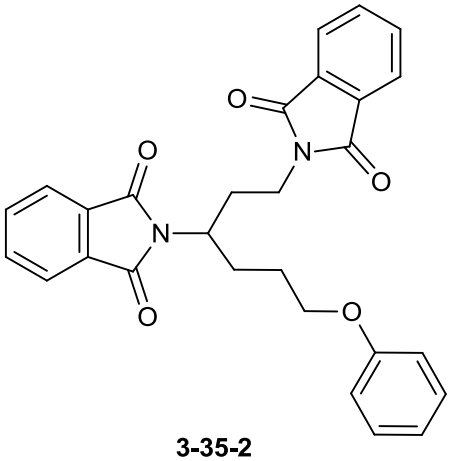
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.85-7.76 (m, 2H, CHPhth), 7.82-7.73 (m, 2H, CHPhth), 7.77-7.68 (m, 2H, CHPhth), 7.74-7.65 (m, 2H, CHPhth), 4.27-4.18 (1H, m, NCH), 3.72-3.63 (m, 2H, NCH_2), 2.62-2.53 (m, 1H, NCH_2CHH), 2.39-2.28 (m, 3H, CH_2CN, NCH_2CHH), 2.28-2.19 (m, 1H, $CHHCH_2CN$), 1.95-1.86 (m, 1H, $CHHCH_2CN$), 1.66-1.57 (m, 2H, $NCHCH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.5 (NCO), 168.2 (NCO), 134.2, 134 (CHPhth), 132, 131.7 (CqPhth), 123.4, 123.3 (CHPhth), 119.1 (CN), 48.3 (NCH), 35.2 (NCH_2), 31.5 (NCH_2CH_2), 30.6 ($NCHCH_2$), 22.5(CH_2CH_2CN), 16.8 (CH_2CN);

IR (CCl_4): νmax 2927, 1776, 1718, 1544, 1468, 1375, 1146, 1070;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{19}N_3O_4$: 401.1376 (401.1380).

2,2'-(6-Phenoxyhexane-1,3-diyl)-bis-(isoindoline-1,3-dione) (3-35-2)



3-35-2

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-34** (100 mg, 0.22 mmol) and allyloxybenzene (44 mg, 0.33 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 68 mg **3-35-2** (yield: 66%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.87-7.78 (m, 2H, CHPhth), 7.81-7.72 (m, 2H, CHPhth), 7.75-7.74 (m, 2H, CHPhth), 7.71-7.63 (m, 2H, CHPhth), 7.22 (dt, 2H, CHAr, J=7.5Hz, J=8.5Hz), 6.88 (t, 1H, CHAr, J=7.3Hz), 6.82 (d, 2H, CHAr, J=7.9Hz), 4.32-4.25 (1H, m, NCH), 3.91 (t, 2H, CH_2OPh, J=1.3Hz, J=6.3Hz), 3.79-3.70 (m, 2H,

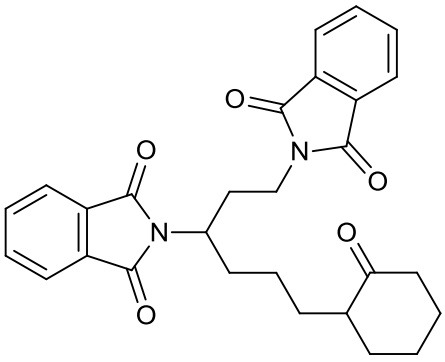
NCH_2), 2.62-2.51 (m, 1H, NCH_2CHH), 2.36-2.27 (m, 1H, NCH_2CHH), 2.27-2.18 (m, 1H, $CHHCH_2OPh$), 1.99-1.91 (m, 1H, $CHHCH_2OPh$), 1.78-1.67 (m, 2H, $NCHCH_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.5, 168.1 (NCO), 158.8 (CqPh), 133.9, 133.8 (CHPhth), 132, 131.8 (CqPhth), 129.3 (CHPh), 123.2, 123.1 (CHPhth), 120.5 (CHPh), 114.4 (CHPh), 67 (CH_2OPh), 49.1(NCH), 35.3 (NCH_2), 30.6 (NCH_2CH_2), 29.1 ($NCHCH_2$), 26.2 (CH_2CH_2O),

IR (CCl_4): νmax 2927, 1774, 1719, 1558, 1374, 1244, 1172, 1078;

HRMS (EI+): *m/z* calculated (found) for $C_{28}H_{24}N_2O_5$: 468.1685 (468.1699).

2,2'-(6-(2-Oxocyclohexyl)hexane-1,3-diyl)bis(isoindoline-1,3-dione) (3-35-3)



3-35-3

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-34** (100 mg, 0.22 mmol) and 2-allylcyclohexanone (46 mg, 0.33 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 64 mg **3-35-3** (yield: 62%) as a colorless oil and a mixture of two diastereoisomers in a ratio 1:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Mixture of diastereoisomer :* δ_H 7.82-7.73 (m, 4H, CHPhth), 7.73-7.62 (m, 4H, CHPhth), 4.25-4.16 (1H, m, NCH), 3.70-3.61 (m, 2H, NCH_2), 2.58-2.49 (m, 1H, NCH_2CHH), 2.29-2.18 (m, 4H, NCH_2CHH, $COCH_2$, COCH), 2.06-1.93 (m, 3H, $COCH_2CHH$, $COCH_2CH_2CHH$, $COCHCH_2CHH$), 1.81-1.54 (m, 6H, $COCH_2CHH$, $COCH_2CH_2CHH$, $COCHCH_2CHH$ $NCHCH_2$,

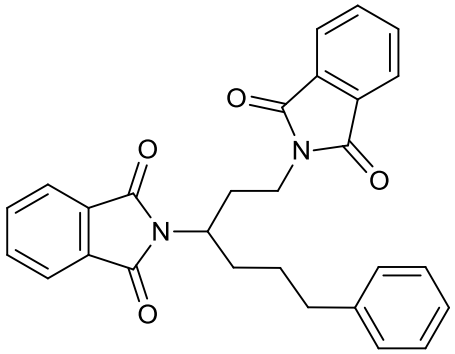
COCH*CH*H), 1.26-1.13 (m, 3H, COCH*CH*H, CHCH$_2$C*H$_2$*);

^{13}C NMR (100 MHz, CDCl$_3$): *Mixture of diastereoisomer :* δ_C 213, 212.9 (CO), 168.6, 168.1 (NCO), 133.9, 133.8 (CHPhth), 132, 131.8 (CqPhth), 123.179, 123.136 (CHPhth), 50.4, 50.3 (NCH), 49.3, 49.2 (CO*C*H), 41.9 (COCH$_2$), 35.3 (NCH$_2$), 34, 33.8 (COCH*C*H$_2$), 32.7, 32.6 (NCH*C*H$_2$), 30.4 (NCH*C*H$_2$CH$_2$N), 29, 28.9 (COCH$_2$*C*H$_2$), 27.97, 27.92 (COCH*C*H$_2$), 24.9, 24.8 (COCH$_2$CH$_2$*C*H$_2$), 24.1, 24 (COCHCH$_2$*C*H$_2$);

IR (CCl$_4$): νmax 2924, 1774, 1717, 1558, 1374, 1251, 1005;

HRMS (EI+): *m/z* calculated (found) for $C_{28}H_{28}N_2O_5$: 472.1998 (472.1998).

2,2'-(6-Phenylhexane-1,3-diyl)bis(isoindoline-1,3-dione) (3-35-4)



3-35-4

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-34** (100 mg, 0.22 mmol) and allylbenzene (39 mg, 0.33 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1) afforded 67 mg **3-35-4** (yield: 68%) as a colorless oil.

^{1}H NMR (400 MHz; CDCl$_3$): δ_H 7.84-7.73 (m, 4H, CHPhth), 7.74-7.65 (m, 4H, CHPhth), 7.26-7.17 (m, 2H, CHAr), 7.15-7.08 (m, 3H, CHAr), 4.30-4.21 (1H, m, NCH), 3.75-3.59 (m, 2H, NCH$_2$), 2.60-2.51 (m, 3H, NCH$_2$C*H*H, CH$_2$Ph), 2.31-2.22 (m, 1H, NCH$_2$CH*H*), 2.16-2.07 (m, 1H, CH*H*CH$_2$Ph), 1.83-1.72 (m, 1H, C*H*HCH$_2$Ph), 1.59-1.51 (m, 2H, NCHC*H$_2$*);

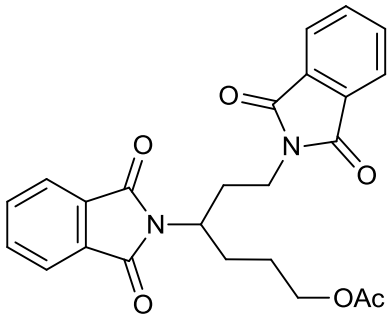
^{13}C NMR (100 MHz, CDCl$_3$): δ_C 168.6, 168.1 (NCO), 141.8 (CqPh), 133.9, 133.8

(CHPhth), 132, 131.8 (CqPhth), 128.32, 128.25 (CHPh), 125.8 (CHPh), 123.2 (CHPhth), 49.1 (NCH), 35.4 (NCH_2), 35.3 (CH_2Ph), 32.1 ($NCH\mathit{C}H_2$), 30.5 ($NCH_2\mathit{C}H_2$), 28.2 ($\mathit{C}H_2CH_2Ph$);

IR (CCl_4): νmax 2928, 1774, 1717, 1558, 1468, 1374, 1172, 1072, 1005;

HRMS (EI+): *m/z* calculated (found) for $C_{28}H_{24}N_2O_4$: 452.1736 (452.1745).

4,6-bis(1,3-Dioxoisoindolin-2-yl)hexyl acetate (3-35-5)



3-35-5

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-34** (82 mg, 0.18 mmol) and allyl acetate (33 mg, 0.33 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1) afforded 55 mg product **3-35-5** (yield: 71%) as a colorless oil.

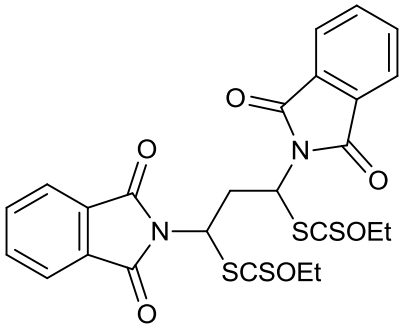
^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.85-7.76 (m, 4H, CHPhth), 7.75-7.66 (m, 4H, CHPhth), 4.29-4.21 (1H, m, NCH), 4.02 (t, 2H, CH_2OAc, J=6.5Hz), 3.64-3.63 (m, 2H, NCH_2), 2.61-2.52 (m, 1H, $NCH_2C\mathit{H}H$), 2.33-2.25 (m, 1H, $NCH_2CH\mathit{H}$), 2.17-2.08 (m, 1H, $CH\mathit{H}CH_2OAc$), 2.0 (s, 3H, OCH_3), 1.88-1.78 (m, 1H, $C\mathit{H}HCH_2OAc$), 1.61-1.52 (m, 2H, $NCHC\mathit{H_2}$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171 ($CO\mathit{C}H_3$), 168.5 (NCO), 168.2(NCO), 134, 133.9 (CHPhth), 132, 131.7 (CqPhth), 123.229, 123.203 (CHPhth), 63.8 (CH_2O), 49 (NCH), 35.2 (NCH_2), 30.5 ($NCH_2\mathit{C}H_2$), 29.1 ($NCH\mathit{C}H_2$), 25.6 ($\mathit{C}H_2CH_2O$), 20.9 (OCH_3);

IR (CCl_4): νmax 2927, 1773, 1712, 1558, 1468, 1365, 1235, 1172, 1038;

HRMS (EI+): *m/z* calculated (found) for $C_{22}H_{19}N_2O_4$ [M-OAc]: 374.1345(374.1352).

Dithiocarbonic acid [1,3-bis-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-ethoxythio -carbony lsulfanyl] ester *O*-ethyl ester (3-36)



3-36

3-5 (3 g, 9.00 mmol), NBS (3.22 g, 18.08 mmol) in CCl_4 (150 ml) was heated at reflux under nitrogen for 3 h; the reaction was initiated by irradiation with a 300 W lamp. The reaction mixture was then cooled, filtered and washed with sodium thiosulfate. After extracting the solution with DCM, the organic layer was concentrated under reduced pressure to yield 3.7 g **3-7** (yield: 85%) without further purification. **3-7** (3.7 g, 7.7 mmol) was dissolved in acetone (2 ml per mmol). KSCSOEt (2.6 g, 16 mmol) was added portion wise over a period of five minutes. It was then left to stir for further half hour before the acetone was evaporated off under reduced pressure. The residue was then taken up in DCM/H_2O and extracted. The DCM layers were dried over Na_2SO_4 before being filtered and evaporated under reduced pressure to yield the crude xanthate. This was then purified by column chromatography using petroleum ether: ethyl acetate, 10:1~2:1 v/v, to obtain 2.6 g **3-36** (72%) and as a mixture of two diastereoisomers in a ratio 1.1:1. One diasereoisomer as a pale yellow solid was crystallized from ethyl acetate/ petroleum ether and another one as yellow oil remained in the solvent.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.88-7.77 (m, 4H, CHPhth), 7.78-7.70 (m, 4H, CHPhth), 6.47 (dt, 2H, J=7.1Hz, J=8.7Hz, CHS), 4.70-4.59 (m, 4H,

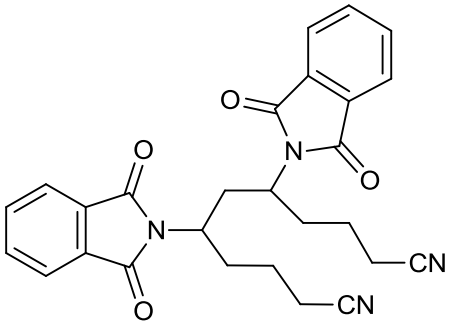
J=7.1Hz, COC*H*$_2$CH$_3$), 3.45-3.34 (m, 1H, CHSC*H*HCHS), 3.21-3.10 (m, 1H, CHSCH*H*CHS), 1.42 (t, 6H, J=7.1Hz, 2COCH$_2$C*H*$_3$) *Diastereoisomer 2*: δ_H 7.88-7.77 (m, 4H, CHPhth), 7.78-7.70 (m, 4H, CHPhth), 6.28-6.19 (m, 2H, CHS), 4.70-4.59 (m, 4H, J=7.1Hz, COC*H*$_2$CH$_3$), 3.30 (dd, 2H, J=8.3Hz, CHSC*H*$_2$CHS), 1.31 (t, 6H, J=7.1Hz, 2COCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): *Diastereoisomer 1*: δ_C 209.7 (C=S), 166.3 (C=O), 134.4 (CPhth), 131.4 (CqPhth), 123.5 (CPhth), 70.7 (O*C*H$_2$), 54.7 (CHS), 36.2 (CH$_2$), 13.6 (OCH$_2$*C*H$_3$);*Diastereoisomer 2*: δ_C 209.6 (C=S), 166.7 (C=O), 134.5 (CPhth), 131.6 (CqPhth), 123.7 (CPhth), 70.6 (O*C*H$_2$), 54 (CHS), 36.1 (CH$_2$), 13.5 (OCH$_2$*C*H$_3$);

IR (CCl$_4$): νmax 2926, 1783, 1724, 1558, 1376, 1226, 1112, 1046;

HRMS (EI+): *m/z* calculated (found) for $C_{22}H_{17}N_2O_5S_2$ [M-SCSOEt]: 453.0579 (453.0573).MP: *Diastereoisomer 1*: 172-173 ℃

5,7-bis(1,3-Dioxoisoindolin-2-yl)undecanedinitrile (3-37-1)

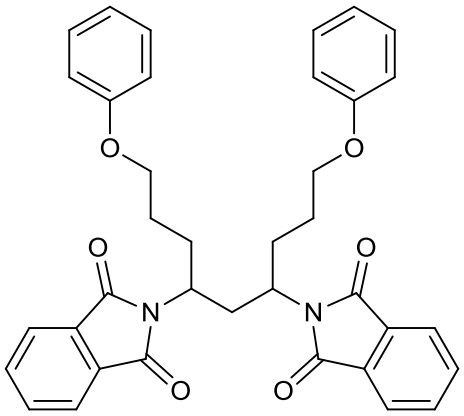


3-37-1

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and allyl cyanide (70 mg, 1.05 mmol), and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 1:1 v/v) afforded 99 mg **3-37-1** (yield: 61%) as a colorless oil and two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.87-7.76 (m, 4H, CHPhth), 7.79-7.70 (m, 4H, CHPhth), 4.09-4.00 (m, 2H, 2NCH), 2.80-2.65 (m, 2H, CHC*H*$_2$CH), 2.28 (t, 4H, J=7.2Hz, 2CH_2CN), 2.18-2.07 (m, 2H, 2C*H*HCH_2CN,), 1.89-1.78 (m, 2H, 2CH*H*CH_2CN), 1.60-1.50 (m, 4H, 2NCHC*H*$_2$); *Diastereoisomer 2*: δ_H 7.67-7.54 (m, 8H, CHPhth), 4.29-4.17 (m, 2H, 2NCH), 2.99-2.88 (m, 1H, CHC*H*HCH), 2.32 (t, 4H, J=7.2Hz, 2CH_2CN), 2.32-2.20 (m, 1H, CHCH*H*CH), 2.28-2.17 (m, 2H, 2C*H*HCH_2CN,), 1.91-1.82 (m, 2H, 2CH*H*CH_2CN), 1.62-1.50 (m, 4H, 2NCHC*H*$_2$);
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.5 (C=O), 134.2 (CPhth), 131.6 (CqPhth), 123.4 (CHPhth), 118.9 (CN), 47.5 (NCH), 33.5 (CH*C*H$_2$CH), 31.9 (CH*C*H$_2$CH$_2$), 22.4 (*C*H$_2$CH$_2$CN), 16.7 (CH$_2$*C*H$_2$CN);*Diastereoisomer 2*: δ_C 168.1 (C=O), 134.1 (CPhth), 131.2 (CqPhth), 123.1 (CHPhth), 119 (CN), 48.8 (NCH), 34.7 (CH*C*H$_2$CH), 31.3 (CH*C*H$_2$CH$_2$), 22.3 (*C*H$_2$CH$_2$CN), 16.6 (CH$_2$*C*H$_2$CN);
IR (CCl_4): νmax 2927, 1773, 1715, 1466, 1377, 1170, 1089;
HRMS (EI+): *m/z* calculated (found) for $C_{27}H_{24}N_4O_4$: 468.1798 (468.1816).

2,2'-(1,9-Diphenoxynonane-4,6-diyl)bis(isoindoline-1,3-dione) (3-37-2)



3-37-2

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and allyloxybenzene (140 mg, 1.05 mmol), and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 112 mg **3-37-2** (yield: 53%) as a colorless oil

and two diastereoisomers in a ratio 2.4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.87-7.74 (m, 4H, CHPhth), 7.78-7.65 (m, 4H, CHPhth), 7.28-7.13 (m, 4H, CHAr), 6.88 (t, 2H, J=7.3Hz, CHAr), 6.79 (d, 4H, J=7.8Hz, CHAr), 4.19-4.08 (m, 2H, 2NCH), 3.86 (t, 4H, J=6.3Hz, $2CH_2OPh$), 2.81-2.72 (m, 2H, J=7.4Hz, J=8.9Hz, CHC*H*$_2$CH), 2.19-2.11 (m, 2H, 2C*H*HCH_2OPh), 1.91 (m, 2H, 2CH*H*CH_2OPh), 1.73-1.62 (m, 4H, 2NCHC*H*$_2$); *Diastereoisomer 2*: δ_H 7.66-7.53 (m, 8H, CHPhth), 7.18-7.07 (m, 4H, CHAr), 6.84 (t, 2H, J=7.3Hz, CHAr), 6.71 (d, 4H, J=7.8Hz, CHAr), 4.31-4.21 (m, 2H, 2NCH), 3.86 (t, 4H, J=6.3Hz, $2CH_2OPh$), 2.98-2.87 (m, 1H, CHC*H*HCH), 2.64-2.51 (m, 1H, CHCH*H*CH), 2.22-2.11 (m, 2H, 2C*H*HCH_2OPh), 1.96-1.87 (m, 2H, 2CH*H*CH_2OPh), 1.76-1.61 (m, 4H, 2NCHC*H*$_2$);

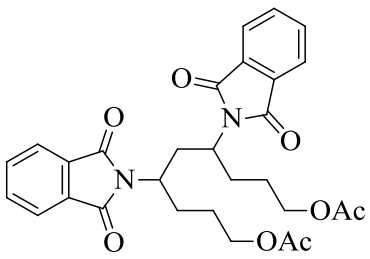
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.7 (C=O), 158.8 (OCqPh), 133.9 (CPhth), 131.8 (CqPhth), 129.3 (CHPh), 123.2 (CHPhth), 120.5 (CHPh), 114.4 (CHPh), 67 (CH_2OPh), 48.4 (NCH), 33.9 (CH*C*H_2CH), 29.5 (CH*C*H_2CH_2), 26.3 (*C*H_2CH_2OPh);

Diastereoisomer 2: δ_C 168.2 (C=O), 158.6 (OCqPh), 133.7 (CPhth), 131.4 (CqPhth), 129.2 (CHPh), 122.8 CHPhth), 120.4 (CHPh), 114.3 (CHPh), 66.8 (CH_2OPh), 48.3 (NCH), 33.7 (CH*C*H_2CH), 29.4 (CH*C*H_2CH_2), 26.2 (*C*H_2CH_2OPh);

IR (CCl_4): νmax 2927, 1774, 1713, 1600, 1497, 1375, 1244, 1172, 1046;

HRMS: *m/z* calculated (found) for $C_{37}H_{34}N_2O_6$ [M-OC_6H_5]: 509.2077 (509.2066).

4,6-bis(1,3-dioxoisoindolin-2-yl)nonane-1,9-diyl diacetate (3-37-2)



3-37-2

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and allyl acetate (105 mg, 1.05 mmol),

and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 105 mg **3-37-2** (yield: 24%) as a colorless oil and as a mixture of two diastereoisomers in a ratio 1.9:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.79 (m, 4H, CHPhth), 7.72 (m, 4H, CHPhth), 4.24 (m, 2H, 2NCH), 3.98 (m, 4H, 2CH_2OAc), 2.70 (m, 2H, J=7.3Hz, J=9.0Hz, $CHCH_2CH$), 2.17 (m, 2H, 2C*H*HCH_2OAc), 1.99 (s, 6H, 2OCH_3), 1.77 (m, 2H, 2CH*H*CH_2OAc), 1.50 (m, 4H, 2NCHC*H*$_2$);

Diastereoisomer 2: δ_H 7.61 (m, 8H, CHPhth), 4.24 (m, 2H, 2NCH), 3.98 (m, 4H, 2CH_2OAc), 2.87 (m, 1H, CHC*H*HCH), 2.26 (m, 1H, CHCH*H*CH), 2.17 (m, 2H, 2C*H*HCH_2OAc), 1.99 (s, 6H, 2OCH_3), 1.77 (m, 2H, 2CH*H*CH_2OAc), 1.50 (m, 4H, 2NCHC*H*$_2$);

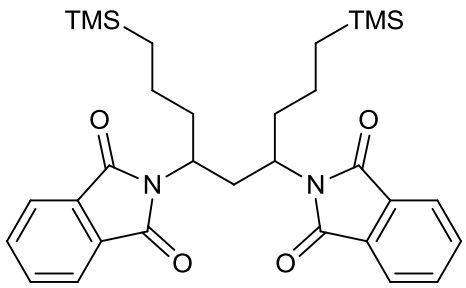
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 170.9 (CH_3*C*=O), 168.6 (C=O), 134 (CPhth), 131.6 (CqPhth), 123.2 (CHPhth), 63.7(*C*H_2OAc), 48.2 (NCH), 33.6 ($CHCH_2CH$), 29.4 ($CHCH_2CH_2$), 25.5 (*C*H_2CH_2OAc), 20.8 (*C*H_3C=O);

Diastereoisomer 2: δ_C 170.8 (CH_3*C*=O), 168.5 (C=O), 133.9 (CPhth), 131.6 (CqPhth), 123.1 (CHPhth), 63.7 (*C*H_2OAc), 48.1 (NCH), 33.5 ($CHCH_2CH$), 29.3 ($CHCH_2CH_2$), 25.5 (*C*H_2CH_2OAc), 20.7 (*C*H_3C=O);

IR (CCl_4): ν_{max} 2928, 1742, 1710, 1554, 1543, 1376, 1238, 1045;

HRMS (EI+): *m/z* calculated (found) for $C_{29}H_{30}N_2O_8$: 534.2002 (534.1995).

2,2'-(1,9-bis(Trimethylsilyl)nonane-4,6-diyl)bis(isoindoline-1,3-dione) (3-37-4)



3-37-4

Following the general procedure A for radical addition, the reaction was carried out

with a solution of **3-36** (200mg, 0.35 mmol) and allyl trimethylsilane (160 mg, 1.4 mmol), and needed 20 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 131 mg **3-37-4** (yield: 67%) as a colorless solid and two diastereoisomers in a ratio 1.9:1.

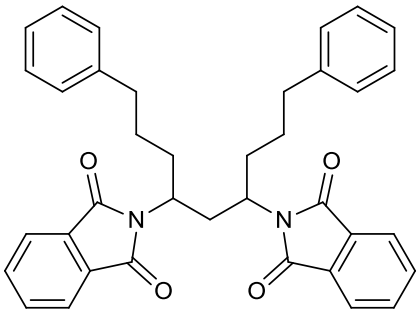
^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.86-7.7- (m, 4H, CHPhth), 7.77-7.65 (m, 4H, CHPhth), 4.13-4.01 (m, 2H, 2NCH), 2.69-2.59 (m, 2H, J=7.5Hz, J=8.8Hz, CH*C*H_2CH), 2.06-1.94 (m, 2H, 2NCHCH*H*), 1.76-1.60 (m, 2H, 2NCHC*H*H), 1.25-1.10 (m, 4H,C$H_2$$CH_2$TMS), 0.48-0.31 (m, 4H, 2CH_2TMS), -0.14 (s, 18H, 2TMS); *Diastereoisomer 2*: δ_H 7.67-7.51 (m, 8H, CHPhth), 4.33-4.18 (m, 2H, 2NCH), 2.91-2.77 (m, 1H, CHC*H*HCH), 2.24-2.11 (m, 1H, CHCH*H*CH), 2.08-1.93 (m, 2H, 2NCHCH*H*), 1.76-1.61 (m, 2H, 2NCHC*H*H), 1.25-1.10 (m, 4H,C$H_2$$CH_2$TMS), 0.57-0.41 (m, 4H, 2CH_2TMS), -0.13 (s, 18H, 2TMS);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.7 (C=O), 133.8 (CPhth), 131.9 (CqPhth), 123.053 (CHPhth), 48.3 (NCH), 36.6 (CH*C*H_2CH), 33.8 (CH*C*$H_2$$CH_2$), 20.716 (*C*$H_2$$CH_2$TMS), 16.1 ($CH_2$*C*$H_2$TMS), -1.8 (TMS);*Diastereoisomer 2*: δ_C 168.6 (C=O), 133.8 (CPhth), 131.7 (CqPhth), 122.8 (CHPhth), 48.2 (NCH), 36.5 (CH*C*H_2CH), 33.7 (CH*C*$H_2$$CH_2$), 20.6 (*C*$H_2$$CH_2$TMS), 16 ($CH_2$*C*$H_2$TMS), -1.8 (TMS);

IR (CCl_4): νmax 2954, 1773, 1712, 1468, 1375, 1249, 1173, 1053;

HRMS (EI+): *m/z* calculated (found) for $C_{31}H_{42}N_2O_4Si_2$: 562.2683 (562.2688).MP: 122~125 ℃

2,2'-(1,9-Diphenylnonane-4,6-diyl)bis(isoindoline-1,3-dione) (3-37-5)



3-37-5

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and allylbenzene (124 mg, 1.05 mmol), and needed 30 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 116 mg **3-37-5** (yield: 58%) as a colorless oil and two diastereoisomers in a ratio 2.1:1.

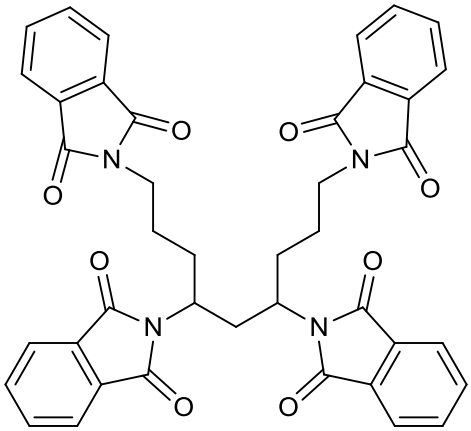
^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.85-7.74 (m, 4H, CHPhth), 7.75-7.68 (m, 4H, CHPhth), 7.25-7.16 (m, 4H, Ar), 7.17-7.08 (m, 2H, Ar), 7.12-7.01 (m, 4H, Ar), 4.14-4.03 (m, 2H, 2NCH), 2.72-2.63 (m, 2H CHC*H*$_2$CH), 2.58-2.47 (m, 4H, 2CH_2Ph), 2.06-1.97 (m, 2H, 2C*H*HCH_2Ph), 1.77-1.66 (m, 2H, 2CH*H*CH_2Ph), 1.53-1.42 (m, 4H, 2NCHC*H*$_2$); *Diastereoisomer 2*: δ_H 7.65-7.52 (m, 8H, CHPhth), 7.25-7.16 (m, 4H, Ar), 7.17-7.08 (m, 4H, Ar), 7.12-7.01 (m, 4H, Ar), 4.48-4.39 (m, 2H, 2NCH), 2.90-2.81 (m, 1H, CHC*H*HCH), 2.58-2.47 (m, 4H, 2CH_2Ph), 2.31-2.22 (m, 1H, CHCH*H*CH), 2.16-2.07 (m, 2H, 2C*H*HCH_2Ph), 1.81-1.72 (m, 2H, 2CH*H*CH_2Ph), 1.57-1.42 (m, 4H, 2NCHC*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.7 (C=O), 133.9 (CPhth), 131.7 (CqPhth), 141.8, 128.3, 128.2, 125.7, 123.1 (Ar), 48.3 (NCH), 35.3 (CH_2Ph), 33.7 (CH*C*H_2CH), 32.4 (CH*C*H_2CH_2), 28.2 (CH_2CH_2Ph); *Diastereoisomer 2*: δ_C 168.6 (C=O), 133.8 (CPhth), 131.7 (CqPhth), 128.3, 125.7, 122.9 (Ar), 48.3 (NCH), 35.3 (CH_2Ph), 33.6 (CH*C*H_2CH), 32.3 (CH*C*H_2CH_2), 28.1 (CH_2CH_2Ph);

IR (CCl_4): νmax 2928, 1709, 1773, 1469, 1376, 1172, 1075;

HRMS (EI+): *m/z* calculated (found) for: $C_{37}H_{34}N_2O_4$: 570.2519 (570.2509).

2,2',2'',2'''-(Nonane-1,4,6,9-tetrayl)tetrakis(isoindoline-1,3-dione) (3-37-6)



3-37-6

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and 2-allylisoindoline-1, 3-dione (196 mg, 1.05 mmol), and add 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 1:1 v/v) afforded 176 mg **3-37-6** (yield: 71%) as a colorless oil and two diastereoisomers in a ratio 2:1.

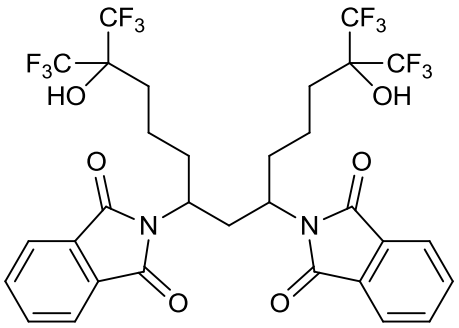
^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.87-7.76 (m, 8H, CHPhth), 7.79-7.68 (m, 8H, CHPhth), 4.14-4.03 (m, 2H, 2NCH), 3.69-3.58 (m, 4H, $2CH_2$NthPh), 2.77-2.65 (m, 2H, CHC*H*$_2$CH), 2.11-2.02 (m, 2H, 2C*H*HCH_2NthPh), 1.79-1.70 (m, 2H, 2CH*H*CH_2 NthPh), 1.61-1.52 (m, 4H, 2NCHC*H*$_2$); *Diastereoisomer 2*: δ_H 7.62-7.43 (m, 16H), 4.29-4.20 (m, 2H, 2NCH), 3.91-3.80 (m, 4H, $2CH_2$NthPh), 2.94-2.84 (m, 1H, CHC*H*HCH), 2.17-2.08 (m, 1H, CHCH*H*CH), 2.11-2.01 (m, 2H, 2C*H*HCH_2NthPh), 1.78-1.69 (m, 2H, 2CH*H*CH_2 NthPh), 1.61-1.53 (m, 4H, 2NCHC*H*$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.6, 168.2 (C=O), 133.9, 133.8 (CPhth), 132, 131.7 (CqPhth), 123.2, 123.1 (CHPhth), 48.1 (NCH), 37.3 (CH_2NthPh), 33.5 (CH*C*H_2CH), 30.1 (CH*C*H_2CH_2), 25.6 (*C*H_2CH_2Phth); *Diastereoisomer 2*: δ_C 168.5, 168.4 (C=O), 133.8, 133.7 (CPhth), 131.9, 131.6 (CqPhth), 123.1, 122.8 (CHPhth), 48 (NCH), 37.2 (CH_2NthPh), 33.4 (CH*C*H_2CH), 30 (CH*C*H_2CH_2), 25.5 (*C*H_2CH_2Phth);

IR (CCl_4): νmax 2927, 1775, 1719, 1469, 1395, 1375, 1264, 1050;

HRMS (EI+): *m/z* calculated (found) for $C_{41}H_{32}N_4O_8$ [M-$C_8H_4NO_2$]: 562.1973 (562.1989).

2,2'-(1,1,1,13,13,13-Hexafluoro-2,12-dihydroxy-2,12-bis(trifluoromethyl)tridecane-6,8-diyl)bis(isoindoline-1,3-dione) (3-37-7)



3-37-7

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and 1,1,1-trifluoro-2-(trifluoromethyl)-pent-4-en-2-ol (218 mg, 1.05 mmol), and add 30 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 141 mg **3-37-7** (yield: 54%) as a colorless oil and two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.89-7.80 (m, 4H, CHPhth), 7.85-7.76 (m, 4H, CHPhth), 4.14-4.04 (m, 2H, 2NCH), 3.60 (s, 2H, CF_3OH), 2.76 (dt, 2H, J=7.4Hz, J=8.9Hz, CHC*H*$_2$CH), 2.08-1.97 (m, 2H, 2C*H*HCH$_2$C$(CF_3)_2$OH), 1.94-1.85 (m, 4H, 2C*H*$_2$C$(CF_3)_2$OH), 1.86-1.75 (m, 2H, 2CH*H*CH$_2$C$(CF_3)_2$OH), 1.58-1.46 (m, 4H, 2NCHC*H*$_2$); *Diastereoisomer 2*: δ_H 7.61-7.51 (m, 8H, CHPhth), 4.25-4.16 (m, 2H, 2NCH), 3.62 (s, 2H, CF_3OH), 2.90-2.81 (m, 1H, CHC*H*HCH), 2.55-2.47 (m, 1H, CHCH*H*CH), 2.06-1.97 (m, 2H, 2C*H*HCH$_2$C$(CF_3)_2$OH), 1.95-1.84 (m, 4H, 2C*H*$_2$C$(CF_3)_2$OH), 1.87-1.76 (m, 2H, 2CH*H*CH$_2$C$(CF_3)_2$OH), 1.57-1.46 (m, 4H, 2NCHC*H*$_2$);

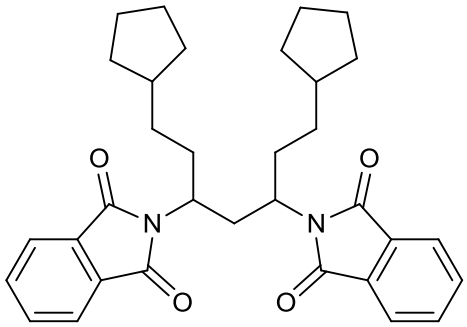
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 169.1 (C=O), 134.3 (CPhth), 131.4 (CqPhth), 122.96 (q, *C*F_3, J=286.8Hz), 123.4 (CHPhth), 76.3, 76.2, 76.2, 76, 75.9, 75.911, 75.7, 75.6 (C$(CF_3)_2$OH), 47.442 (NCH), 32.9 (CH*C*H$_2$CH), 32.7

(CH*C*H_2CH$_2$), 29.2 (*C*H_2CH$_2$C(CF$_3$)$_2$OH), 18.4 (CH$_2$*C*H$_2$ C(CF$_3$)$_2$OH); *Diastereoisomer 2*: δ_C 168.9 (C=O), 134.2 (CPhth), 131.2 (CqPhth), 122.96 (q, *C*F$_3$, J=286.8Hz), 123.3 (CHPhth), 76.3, 76.2, 76.2, 76, 75.9, 75.911, 75.7, 75.6 (C(CF$_3$)$_2$OH), 47.5 (NCH), 32.7 (CH*C*H$_2$CH), 29 (*C*H$_2$CH$_2$C(CF$_3$)$_2$OH), 18.4(CH$_2$*C*H$_2$ C(CF$_3$)$_2$OH);

IR (CCl_4): νmax 2927, 1774, 1717, 1543, 1468, 1376, 1288, 1212;

HRMS (EI+): *m/z* calculated (found) for $C_{31}H_{26}F_{12}N_2O_6$: 750.1599 (750.1614).

2,2'-(1,7-Dicyclopentylheptane-3,5-diyl)bis(isoindoline-1,3-dione) (3-37-8)



3-37-8

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and vinylcyclopentane (134 mg, 1.4 mmol), and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 116 mg **3-37-8** (yield: 63%) as a colorless oil and two diastereoisomers in a ratio 1.9:1.

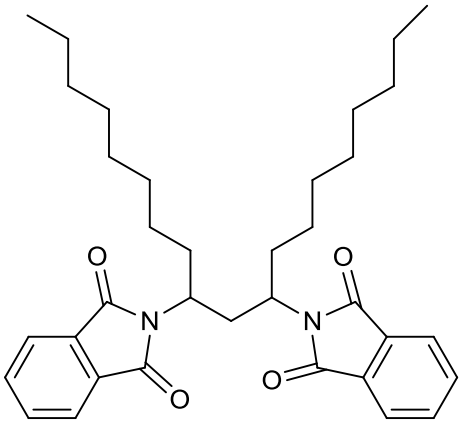
^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.86-7.74 (m, 4H, CHPhth), 7.76-7.66 (m, 4H, CHPhth), 4.06-3.97 (m, 2H, 2NCH), 2.71-2.62 (m, 2H, J=7.6Hz, J=8.7Hz, CHC*H*$_2$CH), 1.99-1.90 (m, 2H, CH$_2$), 1.69-1.61 (m, 7H, 3.5CH$_2$), 1.51-1.39 (m, 7H, 3.5CH$_2$), 1.31-1.19 (m, 4H, 2CH$_2$), 1.13-1.05 (m, 2H, CH$_2$), 0.97-0.86 (m, 4H, 2CH$_2$); *Diastereoisomer 2*: δ_H 7.66-7.54 (m, 8H, CHPhth), 4.26-4.15 (m, 2H, 2NCH), 2.88-2.77 (m, 1H, CHC*H*HCH), 2.29-2.18 (m, 1H, CHCH*H*CH), 2.05-1.94 (m, 2H, CH$_2$), 1.68-1.58 (m, 7H, 3.5CH$_2$), 1.49-1.39 (m, 7H, 3.5CH$_2$), 1.31-1.19 (m, 4H, 2CH$_2$), 1.13-1.05 (m, 2H, CH$_2$), 0.96-0.85 (m, 4H, 2CH$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.8 (C=O), 133.8 (CPhth), 131.8 (CqPhth), 123.1 (CHPhth), 48.9 (NCH), 39.8 (CH), 33.9, 32.7, 32.5, 32.2, 25.2, 25.1, 25.1 (CH_2); *Diastereoisomer 2*: δ_C 168.3 (C=O), 133.7 (CPhth), 131.6 (CqPhth), 122.9 (CHPhth), 50.3 (NCH), 39.6 (CH), 33.7, 32.4, 32.3, 32.1, 25.1, 24.8, 24.6 (CH_2);

IR (CCl_4): νmax 2928, 1773, 1712, 1468, 1375, 1172, 1085;

HRMS (EI+): *m/z* calculated (found) for: $C_{33}H_{38}N_2O_4$: 526.2832 (526.2841).

2,2'-(Nonadecane-9,11-diyl)bis(isoindoline-1,3-dione) (3-37-9)



3-37-9

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and oct-1-ene (157 mg, 1.4 mmol), and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 5:1 v/v) afforded 131 mg **3-37-9** (yield: 67%) as a colorless oil and two diastereoisomers in a ratio 1.7:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.86-7.74 (m, 4H, CHPhth), 7.77-7.66 (m, 4H, CHPhth), 4.08-3.97 (m, 2H, 2NCH), 2.72-2.61 (m, 2H, J=7.5Hz, J=8.9Hz, CHC*H*$_2$CH), 1.99-1.86 (m, 2H, 2CHC*H*HCH$_2$), 1.74-1.61 (m, 2H, 2CHCH*H*CH$_2$), 1.28-1.03(m, 24H, 2$(CH_2)_6$), 0.81 (t, 6H, J=6.9Hz, 2CH_2C*H*$_3$); *Diastereoisomer 2*: δ_H 7.67-7.52 (m, 8H, CHPhth), 4.28-4.15 (m, 2H, 2NCH), 2.90-2.75 (m, 1H, CHC*H*HCH), 2.30-2.17 (m, 1H, CHCH*H*CH), 2.11-1.97 (m, 2H, 2CHC*H*HCH$_2$), 1.77-1.64 (m, 2H, 2CHCH*H*CH$_2$), 1.28-1.03 (m, 24H, 2$(CH_2)_6$), 0.82

(t, 6H, J=6.9Hz, $2CH_2CH_3$);

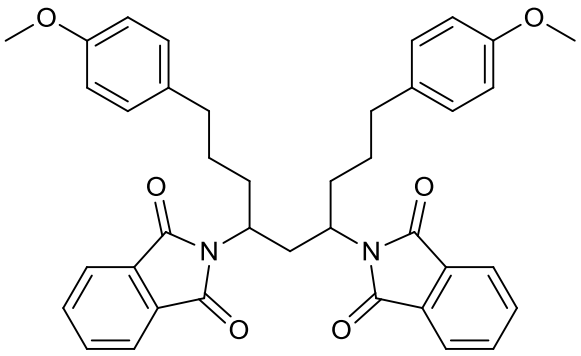
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.8 (C=O), 133.8 (CPhth), 131.8 (CqPhth), 123.1 (CHPhth), 48.8 (NCH), 33.8 ($CHCH_2CH$), 32.9 ($CHCH_2CH_2$), 31.7, 29.3, 29.2, 29.1, 26.4, 22.6 (CH_2), 14 (CH_3);*Diastereoisomer 2*: δ_C 168.3 (C=O), 133.7 (CPhth), 131.6 (CqPhth), 122.9 CHPhth), 48.7 (NCH), 32.9 ($CHCH_2CH$), 32.7 ($CHCH_2CH_2$), 31.6, 29.1, 29, 28.8, 26.3, 22.4 (CH_2), 14 (CH_3);

IR (CCl_4): νmax 2928, 1772, 1709, 1468, 1376, 1172, 1082;

HRMS (EI+): *m/z* calculated (found) for: $C_{35}H_{46}N_2O_4$: 558.3458 (558.3449).

2,2'-(1,9-bis(4-Methoxyphenyl)nonane-4,6-diyl)bis(isoindoline-1,3-dione)

(3-37-10)



3-37-10

Following the general procedure A for radical addition, the reaction was carried out with a solution of **3-36** (200mg, 0.35 mmol) and 4-Allylanisole (155 mg, 1.05 mmol), and needed 25 mol% of DLP to go to completion. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 135 mg **3-37-10** (yield: 61%) as a colorless oil and two diastereoisomers in a ratio 2.5:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H 7.86-7.73 (m, 4H, CHPhth), 7.76-7.66 (m, 4H, CHPhth), 6.96 (d, 4H, J=8.5Hz, Ar), 6.74 (d, 4H, J=8.6Hz, Ar), 4.10-4.01 (m, 2H, 2NCH), 3.74 (s, 6H, $2PhOCH_3$), 2.70-2.61 (m, 2H, $CHCH_2CH$), 2.51-2.41 (m, 4H, $2PhCH_2$), 2.05-1.94 (m, 2H, $2CHHCH_2PhOCH_3$), 1.71-1.62 (m, 2H, $2CHHCH_2PhOCH_3$), 1.62-1.51 (m, 2H, $NCHCH_2$), 1.54-1.43 (m, 2H, $NCHCH_2$);

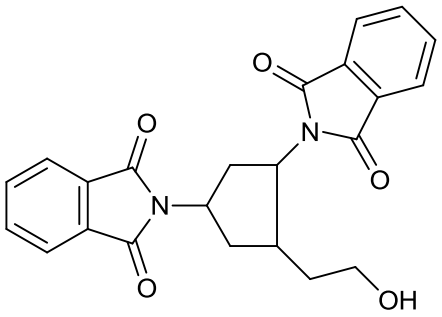
Diastereoisomer 2: δ_H 7.63-7.52 (m, 8H, CHPhth), 6.96 (d, 4H, J=8.6Hz, Ar), 6.73 (d, 4H, J=8.5Hz, Ar), 4.29-4.18 (m, 2H, 2NCH), 3.74 (s, 6H, 2PhOCH_3), 2.91-2.82 (m, 1H, CHC*H*HCH), 2.52-2.41 (m, 4H, 2PhCH_2), 2.30-2.21 (m, 1H, CHCH*H*CH), 2.13-2.04 (m, 2H, 2C*H*HCH_2PhOCH_3), 1.77-1.66 (m, 2H, 2CH*H*CH_2PhOCH_3),1.62-1.51 (m, 2H, NCHCH_2), 1.53-1.42 (m, 2H, NCHCH_2);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C 168.7 (C=O), 133.9 (CPhth), 157.6, 133.8, 131.8, 113.7 (Ar), 129.2 (CqPhth), 123.1 (CHPhth), 55.2 (OCH_3), 48.4 (NCH), 34.4 (CH_2Ph), 33.7 (CHCH_2CH), 32.4 (CHCH_2CH_2), 28.4 (CH_2CH_2Ph); *Diastereoisomer 2*: δ_C 168.6 (C=O), 133.7 (CPhth), 157.5, 133.4, 131.6, 113.6 (Ar), 129.2 (CqPhth), 122.9 (CHPhth), 55.1 (OCH_3), 49.2 (NCH), 34.3 (CH_2Ph), 33.6 (CHCH_2CH), 32.1 (CHCH_2CH_2), 28.4 (CH_2CH_2Ph);

IR (CCl_4): νmax 2929, 1774, 1717, 1513, 1375, 1247, 1176, 1042;

HRMS (EI+): *m/z* calculated (found) for: $C_{39}H_{38}N_2O_6$ [M-$C_8H_5NO_2$]: 483.241 (483.241).

2,2'-(4-(2-Hydroxyethyl)cyclopentane-1,3-diyl)bis(isoindoline-1,3-dione) (3-40)



3-40

Triethylborane (1.0m solution in hexane, 0.14 mmol) was added every 30 minutes over two hours to a stirred solution of **3-36** (200mg, 0.35 mmol) and vinyl epoxide (49mg, 0.7 mmol) in DCM (0.5 ml) under nitrogen at room temperature. During the addition, the syringe needle was lowered into the solution. Furthermore, a small volume of air (about a quarter of the volume of the borane solution) was introduced by syringe following each addition of triethylborane. After stirring the reaction

mixture overnight, the mixture was diluted with DCM and then washed once with water and once with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate: DCM, 10:4:1 v/v) to give 119 mg **3-40** (yield: 84%) as a colorless oil and four diastereoisomers in a ratio 5:4:1:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Major Diastereoisomer 1*: δ_H 7.89-7.79 (m, 4H, CHPhth), 7.75-7.66 (m, 4H, CHPhth), 5.19-5.11 (m, 1H, NC*H*CH), 4.86-4.77 (m, 1H, NC*H*CH_2), 3.68-3.55 (m, 2H, C*H*$_2$OH), 2.85-2.78 (m, 1H), 2.57-2.48 (m, 2H,), 2.33-2.24 (m, 1H, C*H*CH_2CH_2OH), 2.15-2.04 (m, 1H, NCHC*H*HNCH), 1.84-1.75 (m, 1H, NCHCH*H*CH), 1.72-1.63 (m, 1H, C*H*HCH_2OH), 1.37-1.29 (m, 1H, CH*H*CH_2OH); *Major Diastereoisomer 2*: δ_H 7.89-7.79 (m, 4H, CHPhth), 7.75-7.66 (m, 4H, CHPhth), 4.91-4.80 (m, 1H, NC*H*CH), 4.62-4.51 (m, 1H, NC*H*CH_2), 3.67-3.56 (m, 2H, C*H*$_2$OH), 3.43-3.34 (m, 1H, NCHCH*H*NCH), 2.82 (dd, 1H, J=11.4Hz, NCHC*H*HCH), 2.51-2.40 (m, 1H, C*H*CH_2CH_2OH), 2.28-2.17 (m, 1H, NCHC*H*HNCH), 2.13-2.05 (m, 1H, NCHCH*H*CH), 1.74-1.65 (m, 1H, C*H*HCH_2OH), 1.66-1.55 (m, 1H, CH*H*CH_2OH), 1.38 (br, 1H, OH);

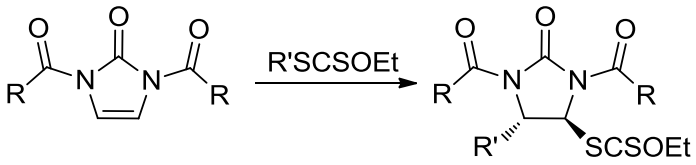
^{13}C NMR (100 MHz, $CDCl_3$): *Major Diastereoisomer 1* δ_C 168.4, 168.2 (C=O), 134, 133.9 (CPhth), 131.98, 131.9 (CqPhth), 123.22, 123.16 (CPhth), 61.4 (*C*H_2OH), 54.5 (N*C*H), 47.7 (N*C*H), 38.9 (*C*H), 35.7 (*C*H_2), 35.2(*C*H_2), 31.9 (*C*H);*Major Diastereoisomer 2*: δ_C 168.8, 168.3 (C=O), 134, 133.9 (CPhth), 131.9, 131.7 (CqPhth), 123.3 123.1 (CPhth), 61.6 (*C*H_2OH), 50.2 (N*C*H), 49.7 (N*C*H), 37.4 (C*H*CH_2CH_2OH), 33.9 (NCH*C*H_2CH), 33 (*C*H_2CH_2OH), 30.5 (*C*H),

IR (CCl_4): νmax 2989, 1756, 1721, 1555, 1438, 1326, 1258;

HRMS (EI+): *m/z* calculated (found) for: $C_{23}H_{20}N_2O_5$: 404.1372 (404.1381).

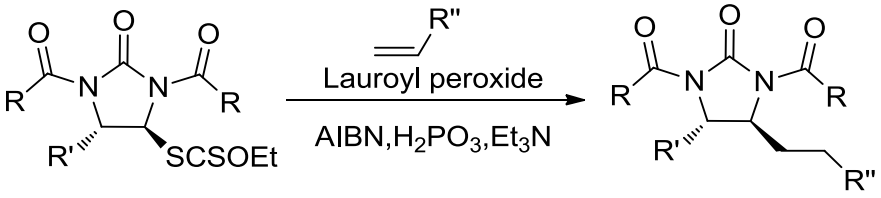
Chapter 4

General procedure A for radical addition



A magnetically stirred solution of xanthate (2~3 equiv) and olefin (1.0 equiv) were dissolved in ethyl acetate (1 ml/mmol of xanthate) was refluxed for 15 min. DLP (5 mol%) was then added and additional DLP (5 mol%) was added every 60 min until total consumption of xanthate. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired compounds. In cases of trisubstituted pyrroles synthesis, the residue could be purified by a quick flash chromatography on silica gel.

General procedure B for radical reduction

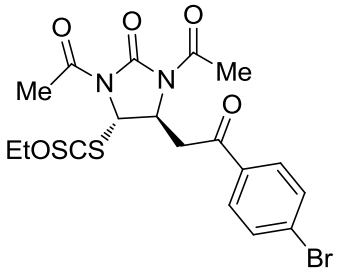


The residue was dissolved in dioxane (10 mL/mmol) then triethylamine (3.3 equiv.) and a solution of H_3PO_2 50% in water (3 equiv.) were added. The solution was refluxed for 15 min and AIBN (10%mol) was then added. After 1 hour, the solution was allowed to cool to room temperature, water and ethyl acetate were added. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to yield the desired compounds.

General procedure C for radical Cyclization

A magnetically stirred solution of the corresponding xanthate (1.0 equiv) in ethyl acetate (0.05 M of xanthate) was refluxed for about 15-30 min under nitrogen. Lauroyl peroxide (DLP) (20% mol) was then added to the refluxing solution every 60 min. The reaction was monitored by TLC every hour until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel to yield the desired compounds.

S-((*4S,5S*)-1,3-Diacetyl-5-(2-(4-bromophenyl)-2-oxoethyl)-2-oxoimidazolidin-4-yl) -O-ethyl carbonodithioate (4-9a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8a** (2.2 g, 7.14 mmol) and **RDC-2** (0.3g, 1.78 mmol), and needed 45 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 0.53g **4-9a** (yield: 62%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.78 (d, 2H, J=8.6Hz, Ar), 7.61 (d, 2H, J=8.6Hz, Ar), 5.84 (d, 1H, J=1.1Hz, C*H*S), 4.85 (m, 1H, NC*H*CH_2), 4.63 (q, 2H, J=7.1Hz, SCSOC*H_2*), 3.78 (dd, 1H, J=5.7Hz, J=17.4Hz, COC*H*H), 3.63 (dd, 1H, J=3.5Hz, J=17.4Hz, COCH*H*), 2.59 (s, 3H, COC*H_3*), 2.51 (s, 3H, COC*H_3*), 1.39 (t, 3H, J=7.1Hz, $SCSOCH_2C$*H_3*);

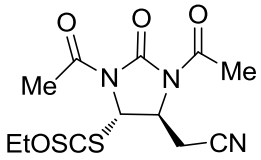
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 210.1 (*C*S), 195.6 (*C*OPhBr), 170.5 (*C*OCH_3), 169.2 (*C*OCH_3), 151.1 (N*C*ON), 134.8, 132.1, 129.5, 129.1 (Ar), 70.2 (SCSO*C*H_2), 62.7 (*C*HS), 57.5 (N*C*HCH_2), 40.7 (CO*C*H_2), 24.3, 24.2 (*C*OCH_3), 13.6

(SCSOCH$_2$*C*H$_3$);

IR (CCl$_4$): νmax 1054, 1244, 1374, 1558, 1704, 1732, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{15}H_{14}BrN_2O_4$: 365.0131 (365.0128).

S-((*4S,5S*)-1,3-Diacetyl-5-(cyanomethyl)-2-oxoimidazolidin-4-yl)-O-ethyl carbonodithioate (4-9b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8b** (2.68g, 18 mmol) and **RDC-2** (1g, 6 mmol), and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 1.5g **4-9b** (yield: 76%) as a white solid.

^{1}H NMR (400 MHz; CDCl$_3$): δ_H ppm 5.77 (s, 1H, C*H*S), 4.58-4.47 (m, 3H, NC*H*CH$_2$, SCSOC*H$_2$*), 3.09-3.01 (m, 2H, CNC*H$_2$*), 2.46 (s, 3H, COC*H$_3$*), 2.41 (s, 3H, COC*H$_3$*), 1.32 (t, 3H, J=7.1Hz, SCSOCH$_2$C*H$_3$*);

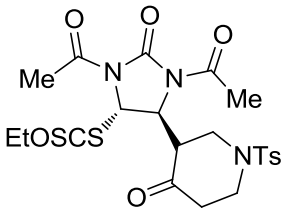
^{13}C NMR (100 MHz, CDCl$_3$): δ_C ppm 209.1 (*C*S), 169.7 (*C*OCH$_3$), 168.2 (*C*OCH$_3$), 149.4 (N*C*ON), 114.8 (CN), 70.2 (SCSO*C*H$_2$), 61.4 (*C*HS), 55.3 (N*C*HCH$_2$), 23.7, 23.5 (*C*OCH$_3$), 21.7 (CN*C*H$_2$), 13.2 (SCSOCH$_2$*C*H$_3$);

IR (CCl$_4$): νmax 1053, 1239, 1344, 1360, 1547, 1713, 1777, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{12}H_{15}N_3O_4S_2$: 329.0504 (329.0516);

MP: 115 - 116 ℃.

S-((*4S,5S*)-1,3-Diacetyl-2-oxo-5-((4-oxo-1-tosylpiperidin-3-yl)methyl)imidazolidin -4-yl) O-ethyl carbonodithioate (4-9c)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8c** (3.3g, 8.9 mmol) and **RDC-2** (0.5g, 2.9 mmol), and needed 55 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 0.86g **4-9c** (yield: 55%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 3:2.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 7.63-7.54 (m, 2H, Ar), 7.32-7.22 (m, 2H, Ar), 5.69-5.62 (s, 1H, C*H*S), 4.66-4.40 (m, 3H, NC*H*CH, SCSOCH_2), 4.05-3.70 (m, 2H, NTsCH_2CH), 3.50-3.20 (m, 2H, NTsCH_2CH$_2$), 2.85-2.75 (m, 2H, NTsCH$_2$CH_2), 2.45-2.32 (m, 10H, 2COCH_3, CH_3, NCHC*H*), 1.34 (t, 3H, J=7.1Hz, SCSOCH$_2$CH_3);

Diastereoisomer 2: δ_H ppm 7.63-7.54 (m, 2H, Ar), 7.32-7.22 (m, 2H, Ar), 5.52-5.46 (s, 1H, C*H*S), 4.66-4.40 (m, 3H, NC*H*CH, SCSOCH_2), 4.05-3.70 (m, 2H, NTsCH_2CH), 3.50-3.20 (m, 2H, NTsCH_2CH$_2$), 2.69-2.55 (m, 3H, NTsCH$_2$CH_2, NCHC*H*), 2.45-2.32 (m, 9H, 2COCH_3, CH_3), 1.26 (t, 3H, J=7.1Hz, SCSOCH$_2$CH_3);

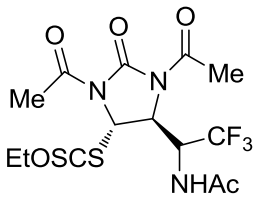
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomers 1:* δ_C ppm 208.2 (CS), 205.1 (CO), 170.2, 169.9 (CO), 150.8 (NCON), 143.8, 132.7, 129.5, 127 (Ar), 70.1 (SCSOCH_2CH$_3$), 62.2 (*C*HS), 58.2 (CONCH), 53.3 (COCH), 48, 45.4 (NCH$_2$), 40.1 (COCH$_2$), 23.9, 23.6 (*C*OCH$_3$), 21 (CH$_3$), 13.2 (SCSOCH$_2$CH_3);

Diastereoisomers 2: δ_C ppm 209 (CS), 204.3 (CO), 168.8, 168.6 (CO), 150.5 (NCON), 143.5, 132.1, 129.4, 126 (Ar), 70 (SCSOCH_2CH$_3$), 61.6 (*C*HS), 58 (CONCH), 49.3 (COCH), 47.3, 45.2 (NCH$_2$), 39.9 (COCH$_2$), 23.7, 23.6 (*C*OCH$_3$), 21 (CH$_3$), 13.1 (SCSOCH$_2$CH_3);

IR (CCl_4): νmax 1053, 1171, 1253, 1369, 1466, 1544, 1559, 1721, 1767, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{19}H_{22}N_3O_6S$: 420.1224 (420.1217).

S-((*4S,5S*)-5-((*R*)-1-Acetamido-2,2,2-trifluoroethyl)-1,3-diacetyl-2-oxoimidazolidin-4-yl) O-ethyl carbonodithioate (4-9d)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8d** (0.93g, 3.57mmol) and **RDC-2** (0.2g, 1.19mmol), and needed 45 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 346 mg **4-9d** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 7.42 (d, 1H, J=9.5Hz, N*H*Ac), 5.86 (d, 1H, J=5.7Hz, C*H*S), 5.43-5.38 (m, 1H, C*H*CF_3), 4.86-4.83 (m, 1H, NC*H*CH), 4.65 (q, 1H, J=7.1Hz, SCSOC*H*$_2$), 2.5 (s, 3H, COC*H*$_3$), 2.46 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$), 1.38 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

Diastereoisomer 2: δ_H ppm 7.81-7.76 (m, 1H, N*H*Ac), 6.08 (d, 1H, J=6.2Hz, C*H*S), 5.22-5.12 (m, 1H, C*H*CF_3), 4.86-4.83 (m, 1H, NC*H*CH), 4.65 (q, 1H, J=7.1Hz, SCSOC*H*$_2$), 2.51 (s, 3H, COC*H*$_3$), 2.48 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$), 1.22 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

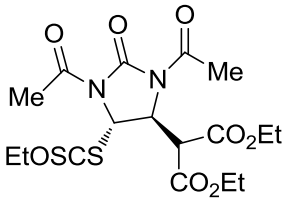
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1:* δ_C ppm 208.4 (*C*S), 171.8, 170.2, 168.7 (*C*OCH_3), 150.1 (N*C*ON), 123.88 (q, J=282.4Hz, *C*F_3), 70.5 (SCSO*C*H_2), 61.3 (*C*HS), 58.2 (NCHCH), 52.39 (q, J=30.4Hz, *C*HCF_3), 24.2, 24.1, 22.4 (CO*C*H_3), 13.5 ($SCSOCH_2CH_3$);

Diastereoisomer 2: δ_C ppm 208.4 (*C*S), 171.8, 170.2, 168.7 (*C*OCH_3), 150.1 (N*C*ON), 123.88 (q, J=282.4Hz, *C*F_3), 70.5 (SCSO*C*H_2), 59.9 (*C*HS), 59.4 (NCHCH), 52.39 (q, J=30.4Hz, *C*HCF_3), 23.9, 23.8, 22.5 (CO*C*H_3), 13.6 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1053, 1137, 1233, 1253, 1347, 1370, 1465, 1506, 1559, 1705, 1774, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{11}H_{13}F_3N_3O_4$: 308.0853 (308.0854).

Diethyl-2-((*4S,5S*)-1,3-diacetyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl)malonate (4-9e)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8e** (0.99g, 3.57mmol) and **RDC-2** (0.2g, 1.19 mmol), and needed 15 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 468 mg **4-9e** (yield: 88%) as a pale yellow oil.

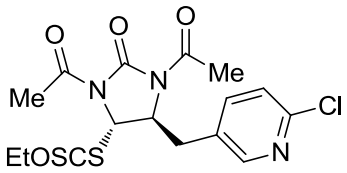
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 5.89 (d, 1H, J=1.6Hz, C*H*S), 5.08-5.01 (m, 1H, NC*H*CH_2), 4.63 (q, 1H, J=7.1Hz, SCSOC*H*$_2$), 4.26-4.18 (m, 5H, 2COC*H*$_2$$CH_3$, C*H*$(CO_2Et)_2$), 2.53 (s, 3H, COC*H*$_3$), 2.50 (s, 3H, COC*H*$_3$), 1.38 (t, 3H, J=7.1Hz, SCSOCH$_2$C*H*$_3$), 1.28-1.18 (m, 6H, 2COCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 208.4 (*C*S), 170.2 (*C*OCH_3), 168.8 (*C*OCH_3), 166 (*C*OCH_2CH_3), 165.8 (*C*OCH_2CH_3), 150.9 (N*C*ON), 70.1 (SCSO*C*H_2), 62.2 (*C*HS), 62.1, 60.8 (CO_2*C*H_2CH_3), 57.4 (N*C*HCH_2), 52.2 (*C*H$(CO_2Et)_2$), 24.3, 24.1 (*C*OCH_3), 13.8 (SCSOCH$_2$*C*H_3), 13.7, 13.5 (CO_2CH_2*C*H_3),

IR (CCl_4): νmax 1053, 1232, 1370, 1553, 1682, 1741, 2855, 2984;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{14}H_{19}N_2O_7$: 327.1187 (327.1192).

_S_-((_4S,5S_)-1,3-Diacetyl-5-((6-chloropyridin-3-yl)methyl)-2-oxoimidazolidin-4-yl)-O-ethyl carbonodithioate (4-9f)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8f** (293mg, 1.19 mmol) and **RDC-2** (80mg, 0.476 mmol), and needed 60 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 106 mg **4-9f** (yield: 54%) as a pale yellow oil.

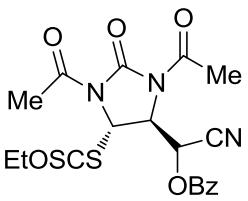
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 8.22 (s, 1H, =C*H*-N=), 7.56-7.48 (m, 1H, -C*H*=), 7.32-7.26 (m, 1H, =C*H*-Cq), 5.84 (s, 1H, C*H*S), 4.77 (t, 2H, J=4.5Hz, NC*H*CH_2), 4.62 (q, 1H, J=7.1Hz, SCSOCH_2), 3.20 (t, 2H, J=5.0Hz, NCHCH_2), 2.56 (s, 3H, COCH_3), 2.21 (s, 3H, COCH_3), 1.40 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 209.6 (*C*S), 170.2, 168.3 (*C*OCH_3), 150.9 (N*C*ON), 150.3, 150, 139.6, 129, 124.2 (Pyridyl), 70.4 (SCSO*C*H_2), 62.2 (*C*HS), 60 (N*C*HCH_2), 34.9 (NCH*C*H_2), 24.3, 23.5 (*C*OCH_3), 13.6 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1053, 1110, 1234, 1248, 1363, 1459, 1711, 1769;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{18}ClN_3O_4S_2$: 415.0427 (415.0443).

(_R_)-Cyano((4S,5S)-1,3-diacetyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl)methyl benzoate (4-9g)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8g** (924mg, 3.29mmol) and **RDC-2** (184mg, 1.09 mmol), and

needed 45 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 332mg **4-9g** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 8.07-8.02 (m, 2H, J=7.1Hz, Ar), 7.51-7.44 (m, 3H, J=7.5Hz, Ar), 6.15 (d, 1H, J=0.6Hz, C*H*CN), 6.12 (d, 1H, J=2.4Hz, C*H*S), 5.08 (d, 1H, J=1.7Hz, NC*H*CH_2), 4.64-4.57 (m, 2H, SCSOC*H*$_2$), 2.62 (s, 3H, COC*H*$_3$), 2.49 (s, 3H, COC*H*$_3$), 1.35 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

Diastereoisomer 2: δ_H ppm 7.91-7.87 (m, 2H, J=7.1Hz, Ar), 7.67-7.61 (m, 3H, J=7.5Hz, Ar), 6.26 (d, 1H, J=0.7Hz, C*H*CN), 6.20 (d, 1H, J=2.5Hz, C*H*S), 5.09 (d, 1H, J=1.1Hz, NC*H*CH_2), 4.82-4.75 (m, 2H, SCSOC*H*$_2$), 2.53 (s, 3H, COC*H*$_3$), 2.35 (s, 3H, COC*H*$_3$), 1.44 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

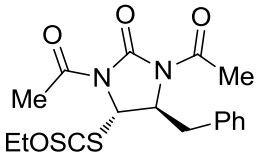
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1:* δ_C ppm 207.3 (*C*S), 170 (O*C*OPh), 168.2, 163.8 (*C*OCH_3), 149.9 (N*C*ON), 134.7, 129.9, 128.9, 126.8 (Ar), 113.5 (*C*N), 70.7 ($SCSOCH_2$), 61 (*C*HS), 59.6 (N*C*HCH_2), 58.8 (CN*C*H), 24, 23.7 (*C*OCH_3), 13.7 ($SCSOCH_2CH_3$);

Diastereoisomer 2: δ_C ppm 207.2 (*C*S), 169.9 (O*C*OPh), 168.2, 163.7 (*C*OCH_3), 149.8 (N*C*ON), 134.6, 129.8, 128.8, 126.8 (Ar), 113.5 (*C*N), 70.6 ($SCSOCH_2$), 61 (*C*HS), 59.5 (N*C*HCH_2), 58.8 (CN*C*H), 23.9, 23.7 (*C*OCH_3), 13.6 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1054, 1085, 1242, 1370, 1453, 1721, 1748, 1773, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{16}H_{14}N_3O_5$: 328.0928 (328.0943).

S-((*4S,5S*)-1,3-Diacetyl-5-benzyl-2-oxoimidazolidin-4-yl)-O-ethylcarbonodithioa--te (4-9h)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8h** (1.48 g, 7.05 mmol) and **RDC-2** (400 mg, 2.35 mmol),

and needed 45 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 498 mg **4-9h** (yield: 56%) as white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.32-7.24 (m, 3H, Ar), 7.19-7.11 (m, 2H, Ar), 5.91 (s, 1H, C*H*S), 4.82-4.74 (m, 1H, NC*H*CH_2), 4.62 (q, 1H, J=7.1Hz, 2H, SCSOC*H*$_2$), 3.28 (dd, 1H, J=4.8Hz, J=14.0Hz, CH*H*Ph), 3.15 (dd, 1H, J=3.0Hz, J=14.0Hz, C*H*HPh), 2.57 (s, 3H, COC*H*$_3$), 1.96 (s, 3H, COC*H*$_3$), 1.41 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

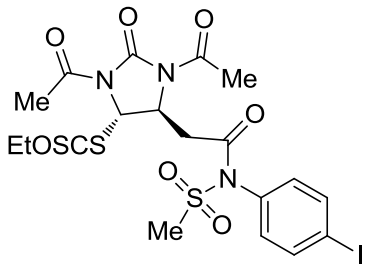
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 210 (*C*S), 170.2, 168.2 (*C*OCH_3), 150.7 (N*C*ON), 134, 129.3, 128.7, 127.4 (Ar), 70.1 (SCSO*C*H_2), 62.1 (*C*HS), 60.3 (N*C*HCH_2), 37.8 (*C*H_2Ph), 24.4, 23.1 (*C*OCH_3), 13.6 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1054, 1240, 1260, 1466, 1558, 1708, 1766, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{14}H_{15}N_2O_3$: 259.1077 (259.1083).

MP: 153~156 ℃.

***S*-((*4S,5S*)-1,3-Diacetyl-5-((4-iodophenyl)(methylsulfonyl)carbamoyl)-2-oxoimidazolidin-4-yl) O-ethyl carbonodithioate (4-9i)**



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8i** (1g, 2.38 mmol) and **RDC-2** (100 mg, 0.6 mmol), and needed 30 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 190 mg **4-9i** (yield: 52%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.81 (d, 1H, J=8.6Hz, Ar), 7.13 (d, 1H,

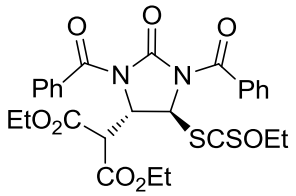
J=8.5Hz, Ar), 5.60 (d, 1H, J=0.6Hz, C*H*S), 4.62-4.57 (m, 2H, SCSOCH_2), 4.52 (t, 1H, J=5.5Hz, NC*H*CH_2), 3.37 (s, 3H, SO_2CH_3), 2.92 (dd, 1H, J=4.8Hz, J=15.5Hz, C*H*HCON), 2.66 (dd, 1H, J=6.4Hz, J=15.5Hz, CH*H*CON), 2.52 (s, 6H, 2CO*C*H_3), 1.36 (t, 1H, J=7.1Hz, $SCSOCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 209.5 (*C*S), 170.7 (*C*ONSO_2Me), 169.3, 169.1 (*C*OCH_3), 150.2 (N*C*ON), 139.4, 134.5, 131.5, 96.8 (Ar), 70.4 (SCSO*C*H_2), 62.7 (*C*HS), 57.1 (N*C*HCH_2), 41.7 (SO_2CH_3), 39.3 (*C*H_2CON), 24.2, 24 (*C*OCH_3), 13.5 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1053, 1229, 1369, 1543, 1558, 1724, 1767, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{20}IN_3O_7S_3$ 612.9508 (612.9515).

Diethyl-2-((*4S,5S*)-1,3-dibenzoyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl)malonate (4-11a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8e** (2.86 g, 10.27 mmol) and **4-10** (0.75 g, 2.57 mmol), and needed 12 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 1.35 g **4-11a** (yield: 92%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.64-7.58 (m, 4H, Ar), 7.50-7.44 (m, 2H, Ar), 7.32-7.40 (m, 4H, Ar), 6.23 (d, 1H, J=2.8Hz, C*H*S), 5.47 (dd, 1H, J=2.9Hz, J=3.7Hz, NC*H*), 4.71 (q, 1H, J=7.1Hz, SCSOC*H*$_2$), 4.35 (d, 1H, J=3.8Hz, C*H*$(CO_2Et)_2$), 4.34-4.20 (m, 4H, 2$CO_2CH_2CH_3$), 1.44 (t, 1H, J=7.1Hz, $SCSOCH_2CH_3$), 1.33 (t, 1H, J=7.1Hz, $CO_2CH_2CH_3$), 1.23 (t, 1H, J=7.2Hz, $CO_2CH_2CH_3$);

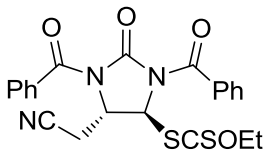
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 208.7 (*C*S), 169.5, 168.1 (*C*OPh), 166.1, 165.9 (*C*OCH_2CH_3), 149.4 (N*C*ON), 133.1, 133, 132.4, 132.2, 129, 129, 127.8, 127.7

(Ar), 70.4 (SCSO*C*H_2), 62.4 (*C*HS), 62.4, 61.9 (CO*C*H_2CH$_3$), 57.4 (N*C*HCH$_2$), 53.3 (*C*H(CO$_2$Et)$_2$), 13.9, 13.8 (COCH$_2$*C*H$_3$), 13.5 (SCSOCH$_2$*C*H$_3$);

IR (CCl$_4$): νmax 1045, 1154, 1228, 1276, 1449, 1693, 1736, 1778, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{24}H_{23}N_2O_7$: 451.1500 (451.1501).

_S_-((_4S,5S_)-1,3-dibenzoyl-5-(cyanomethyl)-2-oxoimidazolidin-4-yl)-O-ethyl carbonodithioate (4-11b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8b** (205 mg, 1.37 mmol) and **4-10** (100 mg, 0.34 mmol), and needed 20 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 130 mg **4-11b** (yield: 85%) as a pale yellow oil.

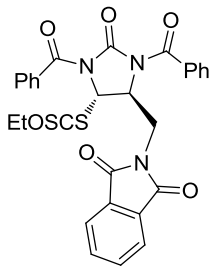
^{1}H NMR (400 MHz; CDCl$_3$): δ_H ppm 7.69 (d, 2H, J=7.2Hz, Ar), 7.61 (d, 2H, J=7.1Hz, Ar) 7.51-7.39 (m, 6H, Ar), 6.07 (d, 1H, J=1.0Hz, C*H*S), 4.96-4.88 (m, 1H, NC*H*CH$_2$), 4.75-4.68 (m, 2H, SCSOC*H*$_2$), 3.58 (dd, 1H, J=4.9Hz, J=17.4Hz, C*H*HCN), 3.24 (dd, 1H, J=2.7Hz, J=17.4Hz, CH*H*CN), 1.47 (t, 3H, J=7.1Hz, SCSOCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ_C ppm 209.7 (*C*S), 169.8, 168 (*C*OPh), 148.7 (N*C*ON), 132.7, 132.5, 132.3, 132.2, 128.8, 128.8, 128, 127.9 (Ar), 115.7 (*C*N), 70.7 (SCSO*C*H$_2$), 64.2 (*C*HS), 57.4 (N*C*HCH$_2$), 22.2 (*C*H$_2$CN), 13.6 (SCSOCH$_2$*C*H$_3$);

IR (CCl$_4$): νmax 1054, 1150, 1213, 1276, 1449, 1699, 1787, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{22}H_{19}N_3O_4S_2$: 453.0817 (453.0829).

***S*-(((*4R,5S*)-1,3-Dibenzoyl-5-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxoimidazolidin-4-yl)methyl) O-ethyl carbonodithioate (4-11c)**



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-8h** (962 mg, 3.42 mmol) and **4-10** (200 mg, 0.68 mmol), and needed 45 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 247 mg **4-11c** (yield: 62%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.89-7.83 (m, 3H, PhthN, Ar), 7.75-7.68 (m, 3H, PhthN, Ar), 7.54-7.50 (m, 2H, Ar), 7.43-7.37 (m, 2H, Ar), 7.36-7.30 (m, 2H, Ar), 7.26-7.20 (m, 2H, Ar), 6.16 (s, 1H, C*H*S), 5.16-5.12 (m, 1H, NC*H*CH_2), 4.71-4.64 (m, 2H, SCSOC*H_2*), 4.48-4.43 (m, 2H, C*H_2*NthPh), 1.45 (t, 3H, J=7.1Hz);

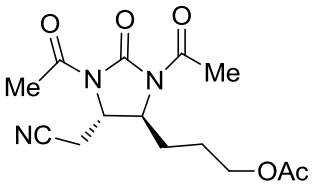
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 209.2 (*C*S), 169.5, 168 (*C*OPh), 167.9 (*C*ON), 149.1 (N*C*ON), 134.3, 134.1 (PhthN), 133, 132.3, 132.1, 131.8, 131.6, 128.7, 128.3, 127.7, 123.6 (Ar), 70.3 (SCSO*C*H_2), 63.2 (*C*HS), 53.4 (N*C*HCH_2), 38.9 (PhthN*C*H_2), 13.6 (SCSOCH$_2$*C*H_3);

IR (CCl_4): νmax 1054, 1233, 1280, 1449, 1544, 1711, 1741, 1774, 2855, 2924, 3031;

HRMS (EI+): *m/z* calculated (found) for $C_{30}H_{25}N_3O_6S_2$: 587.1185 (587.1178).

MP: 232 ~ 234 ℃..

3-((*4S,5S*)-1,3-Diacetyl-5-(cyanomethyl)-2-oxoimidazolidin-4-yl)propylacetate (4-12a)



Following the general procedure A for radical addition and procedure B for removal of xanthate group afford crude **4-12a**. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded **4-12a** (yield: 54%) as a pale yellow oil.

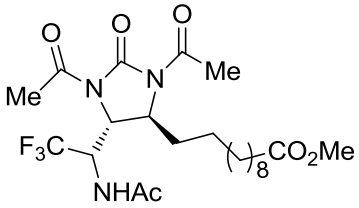
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 4.24-4.20 (m, 2H, 2NC*H*CH_2), 4.05 (t, 2H, J=5.5Hz, C*H*$_2$OAc), 2.84 (dd, 1H, J=6.6Hz, J=16.9Hz, CH*H*CN), 2.75 (dd, 1H, J=3.4Hz, J=16.9Hz, C*H*HCN), 2.53 (s, 3H, COC*H*$_3$), 2.49 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$), 1.88-1.82 (m, 1H, C*H*HCH$_2$OAc), 1.63 (s, 3H, NCHC*H*$_2$, CH*H*CH$_2$OAc);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.8, 170.7, 170 (*C*OCH_3), 150.4 (N*C*ON), 115.3 (*C*N), 63.2 (*C*H$_2$OAc), 55.2 (N*C*H), 51.6 (N*C*H), 29.4 (*C*H$_2$), 24.2, 24.2 (*C*OCH_3), 23.5 (*C*H$_2$CH$_2$CN), 21.8 (*C*H$_2$CN), 20.7 (*C*OCH_3);

IR (CCl_4): νmax 1054, 1145, 1233, 1287, 1454, 1715, 1792, 2845, 2933;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{19}N_3O_5$: 309.1325 (309.1331).

Methyl-11-((*4S,5S*)-5-((*R*)-1-acetamido-2,2,2-trifluoroethyl)-1,3-diacetyl-2-oxoimidazolidin-4-yl)undecanoate (4-12b)



Following the general procedure A for radical addition and procedure B for

removal of xanthate group afford crude **4-12b**. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded **4-12b** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 3:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 7.20 (d, 1H, J=9.9Hz, NH), 5.24-5.18 (m, 1H, CF_3CH), 4.49-4.27 (m, 2H, 2NCH), 3.64 (s, 3H, CO_2CH_3), 2.51 (s, 3H, $COCH_3$), 2.49 (s, 3H, $COCH_3$), 2.28 (t, 2H, J=7.5Hz, CH_2COOCH_3), 1.99 (s, 3H, $COCH_3$), 1.61-1.56 (m, 2H, CH_2), 1.26-1.2 (m, 16H, $8CH_2$);

Diastereoisomer 2: δ_H ppm 6.34 (d, 1H, J=9.9Hz, NH), 4.89-4.82 (m, 1H, CF_3CH), 4.49-4.27 (m, 2H, 2NCH), 3.64 (s, 3H, CO_2CH_3), 2.5 (s, 3H, $COCH_3$), 2.45 (s, 3H, $COCH_3$), 2.28 (t, 2H, J=7.5Hz, CH_2COOCH_3), 1.98 (s, 3H, $COCH_3$), 1.61-1.56 (m, 2H, CH_2), 1.26-1.2 (m, 16H, $8CH_2$);

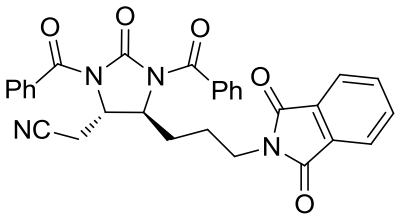
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 174.4, 171.1, 170.4 (CO), 151.1 (NCON), 123.96 (q, J=282.1Hz, CF_3), 68.6 (N*C*HCH), 54.6 (N*C*HCH_2), 51.4 (OCH_3), 51.56 (q, J=31.4Hz, *C*HCF_3), 34.1 (NCH*C*H_2), 29.7, 29.6, 29.5, 29.4 29.3, 29.2, 29.1, 29.1, 29.1 (CH_2), 24.3, 24.2, 23.9 ($COCH_3$), 22.4 ($COOCH_3$);

Diastereoisomer 2: δ_H ppm 172.3, 170.7, 170.3 (CO), 150.8 (NCON), 124.34 (q, J=278.6Hz, CF_3), 66.3 (N*C*HCH), 62.6 (N*C*HCH_2), 52 (OCH_3), 52.45 (q, J=31.4Hz, *C*HCF_3), 32.7 (NCH*C*H_2), 29.7, 29.6, 29.5, 29.4 29.3, 29.2, 29.1, 29.1, 29.1 (CH_2), 24.3, 24.2, 24 ($COCH_3$), 23.9 ($COOCH_3$);

IR (CCl_4): νmax 1138, 1260, 1370, 1706, 1742, 1765, 2855, 2927, 3342;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{36}F_3N_3O_6$: 507.2556 (507.2558).

2-((*4S,5S*)-1,3-Dibenzoyl-5-(3-(1,3-dioxoisoindolin-2-yl)propyl)-2-oxoimidazolidin-4-yl)acetonitrile (4-12c)



Following the general procedure A for radical addition and procedure B for

removal of xanthate group afford crude **4-12c**. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded **4-12c** (yield: 64%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.86-7.83 (m, 2H, Ar), 7.74-7.71 (m, 2H, Ar), 7.6-7.54 (m, 4H, Ar), 7.5-7.43 (m, 2H, Ar), 7.38-7.33 (m, 4H, Ar), 4.53-4.45 (m, 1H, NCH), 4.25-4.21 (m, 1H, NCH), 3.83-3.71 (m, 2H, PhthNCH_2), 3.28 (dd, 1H, J=5.9Hz, J=17.1Hz, CNC*H*H), 2.98 (dd, 1H, J=2.8Hz, J=17.1Hz, CNCH*H*), 2.21-2.16 (m, 1H, CHCH*H*CH_2), 1.93-1.87 (m, 3H, $CHCH_2CH_2$, CHC*H*HCH_2);

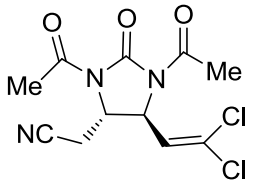
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.2, 169.6, 168.3 (CO), 149.3 (NCON), 134.1, 133.3, 132.8, 132.5, 132, 131.9, 128.9, 128.6, 127.9, 127.9, 123.3 (Ar), 115.6 (CN), 56.5, 53.1 (NCH), 37 (PhthN*C*H_2), 30.2 (NCH*C*H_2CH_2), 23.9 ($NCHCH_2$*C*H_2), 22.1 (CN*C*H_2);

IR (CCl_4): νmax 1233, 1281, 1377, 1466, 1542, 1718, 1776, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) $C_{30}H_{24}N_4O_5$: 520.1747 (520.1739);

MP: 263~265 °C.

2-((*4S,5S*)-1,3-Diacetyl-5-(2,2-dichlorovinyl)-2-oxoimidazolidin-4-yl)acetonitrile (4-13)



A solution of **4-9b** (154 mg, 0.367 mmol) and 1,1-dichloro-2-(ethylsulfonyl)ethane (139 mg, 0.735 mmol) in 0.4 mL chlorobenzene was heated to reflux under N_2 atmosphere for 10 min. To the solution 3 drops of DTBP was added at intervals of 4 h. After refluxing for 12 h, the solution was allowed to cool to room temperature. The solvent was removed under vacuum and the residue was purified via flash chromatography (SiO_2, petroleum ether: ethyl acetate = 4:1) to afford 76 mg **4-13** (yield: 69%) as a yellow oil.

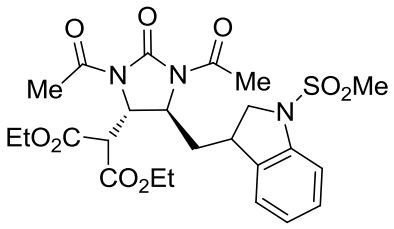
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 5.85 (d, 1H, J=7.9Hz, CH=CCl_2), 4.92 (dd, 1H, J=1.7Hz, J=7.9Hz, NC*H*CH), 4.35-4.32 (m, 1H, NC*H*CH_2), 3.04 (dd, 1H, J=5.8Hz, J=17.1Hz, CNC*H*H), 2.80 (dd, 1H, J=3.1Hz, J=17.1Hz, CNCH*H*), 2.55 (s, 3H, COCH_3), 2.52 (s, 3H, COCH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.4, 169.7 (*C*OCH_3), 149.9 (N*C*ON), 126.4 (*C*Cl_2), 126.3 (*C*=CCl_2), 114.8 (CN), 54.4 (N*C*HCH=), 52.7 (N*C*HCH_2), 24.1, 24 (*C*OCH_3), 21.9 (CN*C*H_2);

IR (CCl_4): νmax 1246, 1367, 1378, 1465, 1559, 1711, 1769, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{11}H_{11}C_{l2}N_3O_3$: 303.0177 (303.0175).

Diethyl-2-((*4S,5S*)-1,3-diacetyl-5-((1-(methylsulfonyl)indolin-3-yl)methyl)-2-oxoimidazolidin-4-yl)malonate (4-15)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-9e** (170 mg, 0.38 mmol) and *N*-allyl-*N*-phenylmethane-sulfonamide (171 mg, 0.76 mmol), and needed 10 mol% of DLP to go to completion. The solution was concentrated in vacuo to obtain the residue which was purified by a quick column to afford 202 mg crude **4-14** (yield: 81%). Then following the procedure C for radical cyclization, a magnetically stirred solution of **4-14** (202 mg, 0.3 mmol) in AcOEt (6.2 ml) was refluxed for about 15-30 min under nitrogen. Lauroyl peroxide (DLP) (20%mol) was then added to the refluxing solution every 60 min. The reaction was monitored by TLC every hour until the starting xanthate was completely consumed. The reaction mixture was then cooled down to room temperature, concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 90 mg **4-15** (yield: 56 %) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 1:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1:* δ_H ppm 7.42-7.36 (m, 1H, Ar), 7.20-7.10 (m, 2H, Ar), 7.04-6.96 (m, 1H, Ar), 4.72-4.66 (m, 1H, NC*H*CH_2), 4.64-4.60 (m, 1H, NC*H*CH), 4.30-4.02 (m, 6H, $2CO_2CH_2CH_3$, C*H*$(CO_2Et)_2$, CH*H*NSO_2Me), 3.92-3.86 (m, 1H, C*H*HNSO_2Me), 3.76-3.70 (m, 1H, C*H*CH_2NSO_2Me), 2.90 (s, 3H, SO_2CH_3), 2.56 (s, 3H, $COCH_3$), 2.47 (s, 3H, $COCH_3$), 2.10-2.04 (m, 1H, CHCH*H*CH), 1.98-1.94 (m, 1H, CHC*H*HCH), 1.25 (m, 6H, $2COCH_2CH_3$);

Diastereoisomer 2: δ_H ppm 7.42-7.36 (m, 1H, Ar), 7.20-7.10 (m, 2H, Ar), 7.04-6.96 (m, 1H, Ar), 4.52-4.46 (m, 1H, NC*H*CH_2), 4.41 (dd, 1H, J=1.1Hz, J=4.0Hz, NC*H*CH), 4.30-4.02 (m, 6H, $2CO_2CH_2CH_3$, C*H*$(CO_2Et)_2$, CH*H*NSO_2Me), 3.82-3.76 (m, 1H, C*H*HNSO_2Me), 3.44-3.36 (m, 1H, C*H*CH_2NSO_2Me), 2.87 (s, 3H, SO_2CH_3), 2.55 (s, 3H, $COCH_3$), 2.41 (s, 3H, $COCH_3$), 1.92-1.88 (m, 2H, $CHCH_2CH$), 1.25 (m, 6H, $2COCH_2CH_3$);

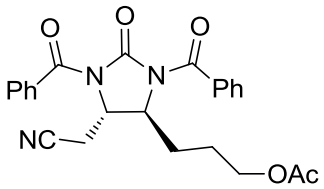
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1:* δ_C ppm 170.9, 170.7 (*C*OCH_3), 166.7, 166.3 (*C*OCH_2CH_3), 151.4 (N*C*ON), 141.6, 134.1, 128.4, 124.4, 123.7, 114.2 (Ar), 62.2, 62.1 ($CO_2CH_2CH_3$), 55.9 (N*C*HCH_2), 55.3 (*C*H$(CO_2Et)_2$), 52.1 (*C*H_2NSO_2Me), 50.9 (N*C*HCH), 41.2 (SO_2CH_3), 36.9 (*C*HCH_2NSO_2Me), 34.6 (CH*C*H_2CH), 24.3, 24 (*C*OCH_3), 13.8, 13.7 ($CO_2CH_2CH_3$);

Diastereoisomer 2: δ_C ppm 170.5, 169.5 (*C*OCH_3), 166.7, 166.3 (*C*OCH_2CH_3), 150.8 (N*C*ON), 141.5, 134, 128.4, 124.2, 123.7, 113.8 (Ar), 62.2, 62.1 ($CO_2CH_2CH_3$), 55.6 (N*C*HCH_2), 54.1 (*C*H$(CO_2Et)_2$), 52 (*C*H_2NSO_2Me), 50.8 (N*C*HCH), 39.1 (SO_2CH_3), 36.3 (*C*HCH_2NSO_2Me), 34.4 (CH*C*H_2CH), 24.2, 23.9 (*C*OCH_3), 13.8, 13.7 ($CO_2CH_2CH_3$);

IR (CCl_4): νmax 1029, 1117, 1165, 1259, 1368, 1558, 1706, 1731, 1747, 1763, 2930, 2984;

HRMS (EI+): *m/z* calculated (found) for $C_{24}H_{31}N_3O_9S$: 537.1781 (537.1778).

3-((*4S,5S*)-1,3-Dibenzoyl-5-(cyanomethyl)-2-oxoimidazolidin-4-yl)propyl acetate (4-18)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-11b** (165 mg, 0.37 mmol) and allyl acetate (75 mg, 0.75 mmol), and needed 10 mol% of DLP to go to completion. The solution was concentrated *in vacuo* to obtain the residue which was used in the next step without purification. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 115 mg **4-18** (yield: 72%) as a white solid.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.62-7.57 (m, 4H, Ar), 7.52-7.45 (m, 2H, Ar), 7.4-7.34 (m, 4H, Ar), 4.52-4.43 (m, 2H, 2NCH), 4.18-4.14 (m, 2H, C*H*$_2$OAc), 3.20 (dd, 1H, J=6.1Hz, J=17.1Hz, CNC*H*H), 2.94 (dd, 1H, J=2.9Hz, J=17.1Hz, CNCH*H*), 2.19-2.13 (m, 1H, NCHCH$_2$C*H*H), 2.06 (s, 3H, $COCH_3$), 1.98-1.93 (m, 1H, NCHCH$_2$CH*H*), 1.85-1.78 (m, 2H, NCHC*H*$_2$CH$_2$);

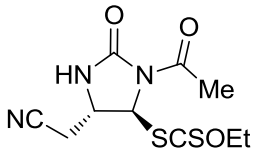
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.9, 170.2, 169.5 (CO), 149.4 (NCON), 133.3, 132.7, 132.6, 132.1, 128.8, 128.5, 128, 127.9 (Ar), 115.6 (CN), 63.3 (CH_2OAc), 56.7, 53 (NCH), 29.3 (NCH*C*H$_2$CH$_2$), 23.7 (CO*C*H$_3$), 22.1 (NCHCH$_2$*C*H$_2$), 20.8 (CN*C*H$_2$);

IR (CCl_4): νmax 1123, 1233, 1281, 1688, 1744, 1777, 2856, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{24}H_{23}N_3O_5$: 433.1638 (433.1641);

MP: 154~155 °C.

S-((*4S,5S*)-3-Acetyl-5-(cyanomethyl)-2-oxoimidazolidin-4-yl)-*O*-ethyl carbonodithioate (4-21)



To a solution of **4-9b** (268 mg, 0.64 mmol) in methanol (1.28 ml) was added DIPEA (83 mg, 0.64 mmol). The reaction was monitored by TLC every hour until the starting material was completely consumed. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) afforded 132 mg **4-21** (yield: 72%) as a pale yellow oil.

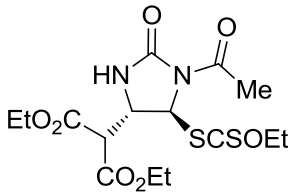
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.96 (br, 1H, N*H*), 5.84 (s, 1H, C*H*S), 4.68-4.61 (m, 2H, SCSOCH_2)), 4.19-4.11 (m, 1H, NC*H*CH_2), 2.97 (dd, 1H, J=3.2Hz, J=16.7Hz, CH*H*CN), 2.85 (dd, 1H, J=7.1Hz, J=16.7Hz, C*H*HCN), 2.49 (s, 3H, COCH_3), 1.42 (t, 3H, J=7.1Hz, $SCSOCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 210.7 (*C*S), 169.1 (*C*OCH_3), 154.2 (N*C*ON), 115.8 (CN), 70.4 (SCSO*C*H_2), 65.3 (*C*HS), 54.5 (N*C*HCH_2), 24.8 (*C*OCH_3), 23.6 (CN*C*H_2), 13.6 ($SCSOCH_2CH_3$);

IR (CCl_4): νmax 1053, 1228, 1307, 1373, 1716, 1771, 2932;

HRMS (EI+): *m/z* calculated (found) for $C_{10}H_{13}N_3O_3S_2$: 287.0398 (287.0404).

Diethyl-2-((*4S,5S*)-1-acetyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl) malonate (4-22)



To a solution of **4-9e** (28 mg, 0.063 mmol) in methanol (0.13 ml) was added DIPEA (8 mg, 0.063 mmol). The reaction was monitored by TLC every hour until the starting material was completely consumed. Flash chromatography on silica gel

(petroleum ether: ethyl acetate, 2:1 v/v) afforded 18mg **4-22** (yield: 74%) as a pale yellow oil.

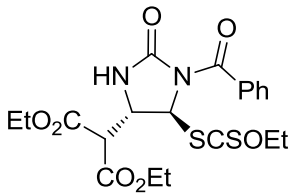
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.10 (s, 1H, N*H*), 5.86 (s, 1H, C*H*S), 4.68-4.61 (m, 2H, SCSOC*H*$_2$), 4.35 (d, 1H, J=4.2Hz, NC*H*CH$_2$), 4.28-4.22 (m, 4H, 2COC*H*$_2$CH$_3$), 3.99 (d, 1H, J=4.2Hz, C*H*(CO$_2$Et)$_2$), 2.47 (s, 3H, COC*H*$_3$), 1.42 (t, 3H, J=7.1Hz, SCSOCH$_2$C*H*$_3$), 1.33-1.26 (m, 6H, J=7.2Hz, 2COCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 210.8 (*C*S), 168.8, 167.2, 166.1 (*C*OCH$_3$), 153.8 (N*C*ON), 70.2 (SCSO*C*H$_2$), 64.2 (*C*HS), 62.5, 62.4 (CO$_2$*C*H$_2$CH$_3$), 57 (N*C*HCH$_2$), 55.4 (*C*H(CO$_2$Et)$_2$), 23.5 (*C*OCH$_3$), 13.9 (SCSOCH$_2$*C*H$_3$), 13.8, 13.7 (CO$_2$CH$_2$*C*H$_3$);

IR (CCl_4): νmax 1023, 1243, 1261, 1712, 1777, 2843, 2922;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{22}N_2O_7S_2$: 406.0868 (406.0861).

Diethyl-2-((*4S,5S*)-1-benzoyl-5-((ethoxycarbonothioyl)thio)-2-oxoimidazolidin-4-yl)malonate (4-23)



To a solution of **4-11a** (895 mg, 1.58 mmol) in methanol (10 ml) was added DIPEA (202 mg, 1.58 mmol). The reaction was monitored by TLC every hour until the starting material was completely consumed. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 1:1 v/v) afforded 576 mg **4-23** (yield: 78%) as a pale yellow oil.

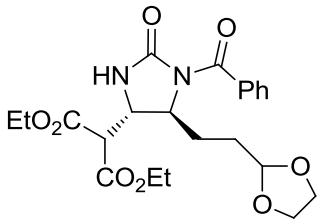
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.62-7.56 (m, 2H, Ar), 7.52-7.46 (m, 1H, Ar), 7.42-7.34 (m, 2H, Ar), 6.28 (s, 1H, C*H*S), 6.23 (br, 1H, N*H*), 4.72-4.62 (m, 2H, SCSOC*H*$_2$), 4.44 (d, 1H, J=3.8Hz, C*H*(CO$_2$Et)$_2$), 4.30-4.10 (m, 4H, 2CO$_2$C*H*$_2$CH$_3$), 4.02-3.98 (m, 1H, NHC*H*CH), 1.43 (t, 3H, J=7.1Hz, SCSOCH$_2$C*H*$_3$), 1.30-1.20 (s, 6H, 2CO$_2$CH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 210.3 (*C*S), 168 (*C*OPh), 166.8, 166 (*C*OCH_2CH_3), 153.2 (N*C*ON), 133.3, 131.7, 128.8, 127.4 (Ar), 70.2 (SCSO*C*H_2), 65.1 (*C*HS), 62.3, 62.3 (CO*C*H_2CH_3), 56.8 (N*C*HCH_2), 55.4 (*C*H$(CO_2Et)_2$), 13.8, 13.8 (COCH_2*C*H_3), 13.5 (SCSOCH_2*C*H_3);

IR (CCl_4): νmax 1054, 1271, 1722, 1777, 2853, 2927;

HRMS (EI+): *m/z* calculated (found) for [M-SCSOEt] $C_{17}H_{19}N_2O_6$: 347.1238 (347.1242).

Diethyl-2-((*4S,5S*)-5-(2-(1,3-dioxolan-2-yl)ethyl)-1-benzoyl-2-oxoimidazolidin-4-yl)malonate (4-24)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **4-23** (312 mg, 0.67 mmol) and 2-vinyl-1,3-dioxolane (134 mg, 1.34 mmol), and needed 10 mol% of DLP to go to completion. The solution was concentrated *in vacuo* to obtain the residue which was used in the next step without purification. The reduction was done following the general procedure B. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 2:1~1:1 v/v) afforded 189 mg **4-24** (yield: 63%) as a colorless oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.56-7.52 (m, 2H, Ar), 7.46-7.42 (m, 1H, Ar), 7.38-7.33 (m, 2H, J=7.5Hz, Ar), 6 (br, 1H, N*H*), 4.90 (t, 1H, J=4.3Hz, OCHO), 4.56-4.53 (m, 1H, NHC*H*), 4.22-4.18 (m, 2H, CO_2C*H*$_2CH_3$), 4.13 (q, 2H, J=7.1Hz, CO_2C*H*$_2CH_3$), 3.96-3.93 (m, 3H, NC*H*CH_2, OCH_2), 3.84-3.82 (m, 2H, OCH_2), 3.55 (d, 1H, J=7.5Hz, C*H*$(CO_2Et)_2$), 2.02-1.91 (m, 2H, CH_2), 1.8-1.75 (m, 2H, CH_2), 1.27 (t, 3H, J=7.1Hz, CO_2CH_2C*H*$_3$), 1.21 (t, 3H, J=7.1Hz, CO_2CH_2C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 169.4 (*C*OPh), 166.6, 166.5 (*C*OCH_2CH_3), 154.1 (N*C*ON), 134.4, 131.1, 128.4, 127.3 (Ar), 103.5 (OCHO), 64.9, 64.8 (OCH_2),

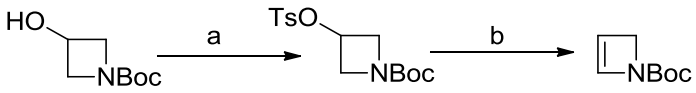
62.1, 62.1 (CO*C*$H_2$$CH_3$), 57.4 (N*C*HCH$_2$), 56.1 (*C*H($CO_2Et)_2$), 52.4 (NH*C*H), 28.3 ($CH_2$), 26.8 ($CH_2$), 13.8, 13.8 (COCH$_2$*C*$H_3$);

IR (CCl_4): νmax 1148, 1241, 1332, 1448, 1670, 1732, 2855, 2927;

HRMS (EI+): *m/z* calculated (found) for $C_{22}H_{28}N_2O_8$: 448.1846 (448.1841).

Chapter 5

Synthetic procedure for N-tert-butylcarbamate-2-azetine 5-3[1]



Reaction conditions: (a) TsCl, pyridine, 0 ℃, (99%). (b) t-BuOK, tBuOH, 80 ℃, (43%).

Step a: 1-Boc-3-hydroxyazetidine (3.4 g, 19.6 mmol, 1 equiv) was dissolved in pyridine (30 mL) and cooled to 0 ℃. After addition of p-toluenesulfonylchloride (7.47 g, 19.6 mmol, 1 equiv), the reaction flask was capped and placed into the freezer for 24 hours. Et_2O and H_2O were then added, and the product extracted three times with Et_2O. The combine organics were washed with 1N HCl (3 times) and brine to provide the desired product as a colorless oil (99% yield), which was used in the following step without further purification.

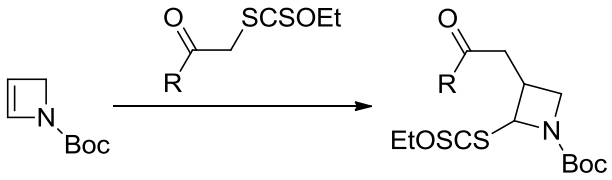
Step b: Under a nitrogen atmosphere, to a solution of tert-butyl 3-(tosyloxy)azetidine -1-carboxylate (3 g, 9.15 mmol, 1 equiv) and t-BuOH (15 mL) was added a solution of t-BuOK (1.029 g, 13.8 mmol, 1.5 equiv) in t-BuOH (30 mL) dropwise via cannulation. The mixture was stirred overnight at 80 ℃. After the reaction was completed, H_2O (60 mL) was added and the mixture was extracted with hexanes (3 times). The hexanes solution was then washed with brine and dried with $MgSO_4$. After removal of the solvent at reduced pressure, the crude oil was purified by silica gel chromatography (elution solvent – pentane:Et_2O = 1:1) to provide 586 mg of a colorless oil (yield: 43%).

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.57 (s, 1H), 5.52 (s, 1H), 4.39 (s, 2H), 1.46 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 151.9, 138.8, 111.9, 58.4, 28.5, 19.5;

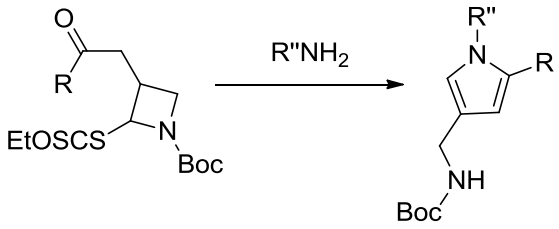
[1] McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R.; *J. Am. Chem. Soc.* **2010**, *132*, 14027.

General procedure A for radical addition



A magnetically stirred solution of xanthate (1 equiv) and olefin (0.8~1.1 equiv) were dissolved in ethyl acetate (1 ml/mmol of xanthate) with several drops of 2,6-lutidine (0.3~0.5 equiv.) was refluxed for 15 min. DLP (5 mol%) was then added and additional DLP (5 mol%) was added every 60 min until total consumption of xanthate. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired compounds.

General procedure B for pyrrole synthesis[2]

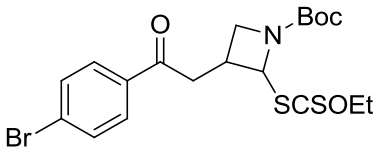


To a solution of xanthate (1 equiv.) in dioxane (5 ml/mmol) were added *p*-toluene sulfonic acid monohydrate (0.5~1 equiv.) and amine (2~4 equiv.). The reaction mixture was refluxed under nitrogen for 0.5~1 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel to give the pyrrole products. In cases of trisubstituted pyrroles synthesis, the residue can be either purified by a column or used in the following step without purification.

[2] Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, *1*, 75.

Adducts 5-6:

Tert-butyl-3-(2-(4-bromophenyl)-2-oxoethyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-6a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5a** (304 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 258 mg **5-6a** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.80 (m, 2H, Ar), 7.60 (m, 2H, Ar), 5.75 (d, 1H, J=4.3Hz, C*H*S), 4.60 (m, 2H, COC*H*$_2$CH$_3$), 4.22 (m, 1H, C*H*HN), 3.70 (m, 1H, CH*H*N), 3.52 (m, 1H,C*H*CHS), 3.37 (m, 1H, COCH*H*), 3.15 (m, 1H, COC*H*H), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 7.80 (m, 2H, Ar), 7.60 (m, 2H, Ar), 6.20 (d, 1H, J=7.5Hz, C*H*S), 4.60 (m, 2H, COC*H*$_2$CH$_3$), 4.22 (m, 1H, C*H*HN), 3.70 (m, 1H, CH*H*N), 3.52 (m, 1H,C*H*CHS), 3.37 (m, 1H, COCH*H*), 3.15 (m, 1H, COC*H*H), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212.4 (*C*=S), 196.7 (*C*O), 154.9 (*C*O), 135.210, 132.110, 129.6, 128.8 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.6 (O*C*H$_2$), 69.9 (CHS), 42.5 (CH$_2$N), 35.8 (CO*C*H$_2$CH), 30.8 (*C*HCH$_2$), 28.3 (OC(CH$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

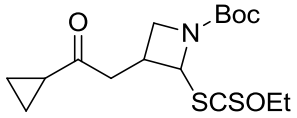
Diastereoisomer 2: δ_C ppm 212.3 (*C*=S), 196.4 (*C*O), 154.8 (*C*O), 135, 132, 129.6, 128.6 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.7 (CHS), 39.8 (CH$_2$N), 35.8 (CO*C*H$_2$CH), 29.7 (*C*HCH$_2$), 28.4 (OC(CH$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1113, 1149, 1230, 1273, 1367, 1391, 1470, 1484, 1541, 1558,

1586, 1691, 1707, 1726, 2927,2960, 2983;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{16}H_{19}BrNO_3$: 352.0543 (352.0546).

Tert-butyl-3-(2-cyclopropyl-2-oxoethyl)-2-((ethoxycarbonothioyl)thio)azetidine-1 - carboxylate (5-6b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5b** (301 mg, 0.84 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (142 mg, 0.7 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 221 mg **5-6b** (yield: 74%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.65 (d, 1H, J=3.7Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.44 (m, 2H, CH*H*N, C*H*CHS), 2.98 (m, 2H, COC*H*$_2$), 1.90 (m, 1H, CH$_2$C*H*), 1.39 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 0.97 (m, 2H, C*H*$_2$CH), 0.86 (m, 2H, C*H*$_2$CH);

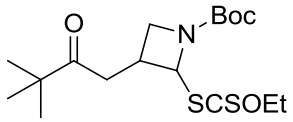
Diastereoisomer 2: δ_H ppm 6.11 (d, 1H, J=7.1Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.44 (m, 2H, CH*H*N, C*H*CHS), 2.98 (m, 2H, COC*H*$_2$), 1.90 (m, 1H, CH$_2$C*H*), 1.39 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 0.97 (m, 2H, C*H*$_2$CH), 0.86 (m, 2H, C*H*$_2$CH);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212.1 (*C*=S), 208.2 (*C*O), 154.8 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.6 (O*C*H$_2$), 69.7 (*C*HS), 46.9 (*C*H$_2$N), 35.5 (CO*C*H$_2$CH), 30.4 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 20.8 (*C*HCH$_2$), 13.8 (OCH$_2$*C*H$_3$), 11.1 (*C*H$_2$CH);

Diastereoisomer 2: δ_C ppm 211.8 (*C*=S), 208 (*C*O), 154.9 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.6 (*C*HS), 44.3 (*C*H$_2$N), 35.5 (CO*C*H$_2$CH), 30.4 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 20.7 (*C*HCH$_2$), 13.8 (OCH$_2$*C*H$_3$), 11 (*C*H$_2$CH);

IR (CCl_4): νmax 1048, 1149, 1226, 1368, 1464, 1539, 1543, 1718, 1786, 2876, 2933;
HRMS (EI+): *m/z* calculated (found) for *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{13}H_{20}NO_3$: 238.1438 (238.1446).

Tert-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-((ethoxycarbonothioyl)thio)azetidine-1-carboxylate (5-6c)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5c** (176 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (103 mg, 0.66 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 203mg **5-6c** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 6.12 (d, 1H, J=7.3Hz C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.39 (m, 1H, C*H*HN), 3.16 (m, 1H, C*H*CHS), 2.89 (m, 2H, COC*H*$_2$), 1.38 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.11 (s, 9H, (C*H*$_3$)$_3$);

Diastereoisomer 2: δ_H ppm 5.62 (d, 1H, J=4.1Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.39 (m, 1H, C*H*HN), 3.16 (m, 1H, C*H*CHS), 2.89 (m, 2H, COC*H*$_2$), 1.38 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.09 (s, 9H, (C*H*$_3$)$_3$);

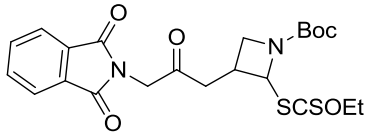
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 213.8 (*C*=S), 212.2 (*C*O), 154.9 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.8 (CHS), 44.1 (*C*H$_2$N), 40.5 (CO*C*H$_2$CH), 30.6 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 26.5 (C(*C*H$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 213.6 (*C*=S), 211.6 (*C*O), 154.7 (*C*O), 80.6 (O*C*(CH$_3$)$_3$), 72.3 (O*C*H$_2$), 69.6 (CHS), 43.9 (*C*H$_2$N), 37.8 (CO*C*H$_2$CH), 30.6 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 26.4 (C(*C*H$_3$)$_3$), 13.7 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1049, 1114, 1148, 1223, 1367, 1391, 1464, 1501, 1712, 1783, 2872, 2970;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{14}H_{24}NO_3$: 254.1751 (254.1752).

Tert-butyl-3-(3-(1,3-dioxoisoindolin-2-yl)-2-oxopropyl)-2-((ethoxycarbonothioyl) thio)azetidine-1-carboxylate (5-6d)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5d** (310 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 338 mg **5-6d** (yield: 74%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.84 (m, 2H, PhthN), 7.73 (m, 2H, PhthN), 6.12 (d, 1H, J=7.2Hz, C*H*S), 4.61 (m, 2H, J=7.1Hz, COC*H*$_2$CH$_3$), 4.49 (m, 2H, PhthNC*H*$_2$), 4.11 (m, 1H, C*H*HN), 3.51 (m, 2H, CH*H*N, C*H*CHS), 2.99 (m, 2H, COC*H*$_2$), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 7.84 (m, 2H, PhthN), 7.73 (m, 2H, PhthN), 5.67 (d, 1H, J=3.9Hz, C*H*S), 4.61 (m, 2H, J=7.1Hz, COC*H*$_2$CH$_3$), 4.49 (m, 2H, PhthNC*H*$_2$), 4.11 (m, 1H, C*H*HN), 3.51 (m, 1H, CH*H*N), 3.30 (m, 1H, C*H*CHS), 2.99 (m, 2H, COC*H*$_2$), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

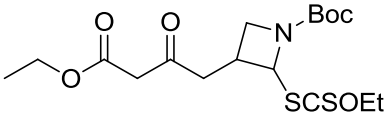
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 211.9 (*C*=S), 200.1 (*C*O), 167.5 (*C*O), 154.7 (*C*O), 134.2, 131.9, 123.6 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.3 (*C*HS), 69.8 (O*C*H$_2$), 53.6 (*C*H$_2$N), 46.5 (PhthN*C*H$_2$), 43.5 (C*H*CHS), 40.9 (COC*H*$_2$), 28.2 (OC(*C*H$_3$)$_3$), 13.7 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 211.5 (*C*=S), 199.9 (*C*O), 167.5 (*C*O), 154.6 (*C*O), 134.19, 131.9, 123.5 (Ar), 80.825, 80.79 (O*C*(CH$_3$)$_3$), 72.2 (CHS), 69.7(O*C*H$_2$), 53.2 (*C*H$_2$N), 46.4 (PhthN*C*H$_2$), 43.5 (C*H*CHS), 40.9 (COC*H*$_2$), 30.1 (C*H*CHS), 28.2 (OC(*C*H$_3$)$_3$), 13.69 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1111, 1145, 1219, 1313, 1368, 1390, 1415, 1456, 1547, 1558, 1724, 1779, 2899, 2929, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{19}H_{21}N_2O_5$: 357.1445 (357.1442).

Tert-butyl-3-(4-ethoxy-2,4-dioxobutyl)-2-((ethoxycarbonothioyl)thio)azetidine-1-carboxylate (5-6g)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5g** (240 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 264 mg **5-6g** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1, which could be separated.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.64 (d, 1H, J=3.2Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.15 (m, 3H, C*H*HN, COOC*H*$_2$CH$_3$), 3.45 (m, 3H, CH*H*N, COC*H*$_2$CO), 3.27 (m, 1H, C*H*CHS), 3.01 (m, 2H, COC*H*$_2$), 1.40 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.27 (t, 3H, J=7.2Hz, COOCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 5.68 (d, 1H, J=3.2Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.15 (m, 3H, C*H*HN, COOC*H*$_2$CH$_3$), 3.45 (m, 3H, CH*H*N, COC*H*$_2$CO), 3.27 (m, 1H, C*H*CHS), 3.01 (m, 2H, COC*H*$_2$), 1.40 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.28 (t, 3H, J=7.2Hz, COOCH$_2$C*H*$_3$);

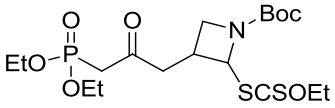
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212 (*C*=S), 200.3 (*C*O), 166.8 (*C*O), 154.6 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.2 (O*C*H$_2$), 69.6 (*C*HS), 61.5 (COCH$_2$CH$_3$), 49.1 (COCH$_2$CO), 46.4 (*C*H$_2$N), 35.2 (*C*HCH$_2$), 28.2 (OC(*C*H$_3$)$_3$), 14 (COCH$_2$*C*H$_3$), 13.7 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 212.3 (*C*=S), 200.5 (*C*O), 166.9 (*C*O), 154.8 (*C*O), 80.9 (O*C*(CH$_3$)$_3$), 72.4 (O*C*H$_2$), 69.7 (*C*HS), 61.5 (COCH$_2$CH$_3$), 49.2 (COCH$_2$CO), 46.7 (*C*H$_2$N), 35.3 (*C*HCH$_2$), 28.2 (OC(*C*H$_3$)$_3$), 14.1 (COCH$_2$*C*H$_3$), 13.8 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1111, 1147,1223, 1321, 1367, 1390, 1456, 1477, 1538, 1713, 2856, 2900, 2930, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{14}H_{22}NO_5^+$: 284.1492 (284.1498).

Tert-butyl-3-(3-(diethoxyphosphoryl)-2-oxopropyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-6e)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5e** (314 mg, 1 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 318 mg **5-6e** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.61 (d, 1H, J=4.4Hz, C*H*S), 4.57 (m, 2H, COC*H*$_2$CH$_3$), 4.10 (m, 5H, C*H*HN, 2OC*H*$_2$CH$_3$), 3.42 (m, 1H, CH*H*N), 3.28 (m, 1H, C*H*CHS), 3.03 (m, 4H, COC*H*$_2$CH, POC*H*$_2$CO), 1.37 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.29 (t, 6H, J=7.0 Hz, 2OCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 6.07 (d, 1H, J=7.2Hz, C*H*S), 4.57 (m, 2H, COC*H*$_2$CH$_3$), 4.10 (m, 5H, C*H*HN, 2OC*H*$_2$CH$_3$), 3.42 (m, 1H, CH*H*N), 3.28 (m, 1H, C*H*CHS), 3.03 (m, 4H, COC*H*$_2$CH, POC*H*$_2$CO), 1.37 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.29 (t, 6H, J=7.0 Hz, 2 OCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 211.8 (*C*=S), 199.4 (*C*O), 154.6 (*C*O), 80.5 (O*C*(CH$_3$)$_3$), 72.0 (*C*HS), 69.6 (O*C*H$_2$), 62.65, 62.63 (OC*H*$_2$CH$_3$), 52.4 (*C*H$_2$N), 47.2 (*C*HCHS), 44.7 (POC*H*$_2$CO), 41.8 (COCH$_2$CH), 28.1(OC(*C*H$_3$)$_3$), 16.2 (COCH$_2$*C*H$_3$), 13.6 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 211.5 (*C*=S), 199.3 (*C*O), 154.5 (*C*O), 80.5 (O*C*(CH$_3$)$_3$), 72.0 (*C*HS), 69.4 (O*C*H$_2$), 62.58, 62.56 (OC*H*$_2$CH$_3$), 47.2 (*C*HCHS), 43.1 (POC*H*$_2$CO), 35.0 (COCH$_2$CH), 30.1 (*C*H$_2$N), 28.1(OC(*C*H$_3$)$_3$), 16.1 (COCH$_2$*C*H$_3$),

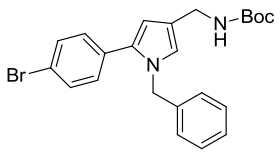
13.5 (OCH_2CH_3);

IR (CCl_4): νmax 1055, 1111, 1147, 1219, 1367, 1391, 1443, 1456, 1478, 1502, 1712, 2931, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{15}H_{27}NO_6P$: 348.1571 (348.1576).

Synthesis of pyrroles

Tert-butyl-((1-benzyl-5-(4-bromophenyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7a)



To a solution of **5-6a** (130 mg, 0.28 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (24 mg, 0.14 mmol) and benzylamine (62 mg, 0.56 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 106 mg **5-7a** (yield: 87%) as a pale yellow oil.

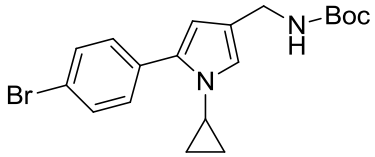
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 (d, 2H, J=8.4Hz, C*H*ArBr), 7.29 (m, 3H, Ar), 7.14 (d, 2H, J=8.4Hz, C*H*ArBr), 6.99 (d, 2H, J=7.0Hz, Ar), 6.68 (s, 1H, NC*H*=), 6.20 (s, 1H, C*H*), 5.05 (s, 2H, NCH_2Ph), 4.73 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=4.9Hz, CH_2NHBoc), 1.45 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.7 (*C*O), 138.2 (=*C*-Ph), 133.9, 131.9, 131.7, 130.4, 128.7, 127.4, 127.6, 126.2 (*C*HAr), 121.4 (=*C*-), 121.1 (N*C*H=), 108.9 (*C*H), 79.1 (O*C*$(CH_3)_3$), 50.5 (*C*H_2Ph), 37.6 (*C*H_2NHBoc), 28.3 (OC$(CH_3)_3$);

IR (CCl_4): νmax 1011, 1073, 1170, 1245, 1366, 1391, 1467, 1497, 1544, 1547, 1718, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{25}BrN_2O_2$: 440.1099 (440.1096).

Tert-butyl ((5-(4-bromophenyl)-1-cyclopropyl-1H-pyrrol-3-yl)methyl)carbamate (5-7b)



To a solution of **5-6a** (60 mg, 0.13 mmol) in dioxane (0.65 ml) were added *p*-toluene sulfonic acid monohydrate (10 mg, 0.05 mmol) and cyclopropylamine (14 mg, 0.25 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 47 mg **5-7b** (yield: 93%) as a pale yellow oil.

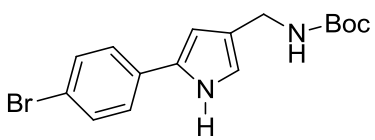
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.54 (d, 2H, J=8.4Hz, Ar), 7.43 (d, 2H, J=8.4Hz, Ar), 6.77 (s, 1H, NC*H*=), 6.20 (s, 1H，C*H*), 4.72 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=5.0Hz, CH_2NHBoc), 3.40 (m, 1H, NC*H*), 1.51 (s, 9H, Boc), 0.92 (m, 2H, CHCH_2), 0.83 (m, 2H, CHCH_2);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 134.4 (=*C*-Ph), 132.2, 131.2, 129.6, 121.4 (Ar), 121.4 (=*C*-), 120.5 (N*C*H=), 108.7 (*C*H), 79.2 (O*C*(CH_3)$_3$), 37.6 (*C*H_2NHBoc), 29.5 (N*C*H), 28.4 (OC(CH_3)$_3$), 8.4 (NCH*C*H_2);

IR (CCl_4): νmax 1012, 1030, 1074, 1171, 1244, 1366, 1391, 1456, 1498, 1716, 2855, 2928, 2979, 3007, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{23}BrN_2O_2$: 390.0943 (390.0956).

Tert-butyl ((5-(4-bromophenyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7c)



To a solution of **5-6a** (90 mg, 0.2 mmol) in dioxane (1.4 ml) were added

ammonium acetate (16 mg, 0.2 mmol) and aqua ammonia (20% NH_3) (32 mg, 0.38 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 66 mg **5-7c** (yield: 95%) as a pale yellow oil.

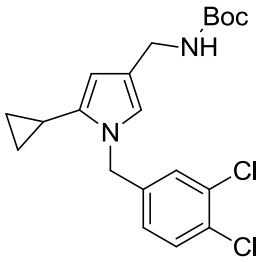
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.61 (br, 1H, N*H*), 7.50 (d, 2H, J=8.4Hz, Ar), 7.36 (d, 2H, J=8.4Hz, Ar), 6.80 (s, 1H, NC*H*=), 6.49 (s, 1H, CH), 4.80 (br, 1H, N*H*Boc), 4.24 (d, 2H, J=4.8Hz, CH_2NHBoc), 1.51 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.9 (*C*O), 131.8 (=*C*-Ph), 131.5, 131.4, 125.2, 122.9, 119.7 (=*C*-), 117.6 (N*C*H=), 106.1 (*C*H), 79.2 (O*C*(CH_3)$_3$), 37.7 (CH_2NHBoc), 28.4 (OC(*C*H_3)$_3$),

IR (CCl_4): νmax 1009, 1075, 1171, 1237, 1366, 1472, 1498, 1548, 1558, 1718, 2360, 2343, 2855, 2927, 3481;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{19}BrN_2O_2$: 350.0630 (350.0623).

Tert-butyl((5-cyclopropyl-1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7d)



To a solution of **5-6b** (31 mg, 0.09 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and 3,4-dichloro-benzylamine (32mg, 0.18 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 32 mg **5-7d** (yield: 91%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (d, 1H, J=8.4Hz, Ar), 7.14 (s, 1H, Ar), 6.84 (d, 1H, J=8.0Hz, Ar), 6.50 (s, 1H, NC*H*=), 5.78 (s, 1H, C*H*), 5.06 (s, 2H,

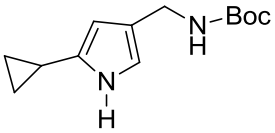
NC*H*$_2$Ar), 4.62 (br, 1H, N*H*Boc), 4.11 (d, 2H, J=4.7Hz, C*H*$_2$NHBoc), 1.45 (s, 9H, Boc), 0.90 (m, 1H, C*H*CH$_2$), 0.73 (m, 2H, CHC*H*$_2$), 0.52 (m, 2H, CHC*H*$_2$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 135.8 (=*C*-), 138.9, 132.9, 131.5, 130.7, 128.6, 125.9 (Ar), 120.3 (=*C*-), 118.9 (N*C*H=), 105.6 (*C*H), 79.2 (O*C*(CH$_3$)$_3$), 49.3 (N*C*H$_2$), 37.9 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 6.8 (*C*HCH$_2$), 6.1 (CH*C*H$_2$);

IR (CCl$_4$): νmax 1032, 1046, 1172, 1391, 1423, 1471, 1495, 1718, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{24}Cl_2N_2O_2$: 394.1215 (394.1219).

Tert-butyl ((5-cyclopropyl-1H-pyrrol-3-yl)methyl)carbamate 5-7e



To a solution of **5-6b** (31 mg, 0.09 mmol) in dioxane (0.5 ml) were added ammonium acetate (7 mg, 0.09 mmol) and aqua ammonia (20% NH$_3$) (23 mg, 0.27 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 19 mg **5-7e** (yield: 91 %) as a pale yellow oil.

^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 7.88 (br, 1H, N*H*), 6.54 (s, 1H, NC*H*=), 5.80 (s, 1H，C*H*), 4.62 (br, 1H, N*H*Boc), 4.12 (d, 2H, J=4.9Hz, C*H*$_2$NHBoc), 1.76 (m, 1H, C*H*CH$_2$), 1.45 (s, 9H, Boc), 0.80 (m, 2H, CHC*H*$_2$), 0.59 (m, 2H, CHC*H*$_2$);

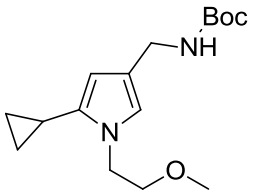
^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 135.1 (=*C*-), 114.3 (=*C*-), 114.2 (N*C*H=), 103.9 (*C*H), 79.1 (O*C*(CH$_3$)$_3$), 37.9 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 8.2 (*C*HCH$_2$), 6.5 (CH*C*H$_2$);

IR (CCl$_4$): νmax 1053, 1170, 1367, 1391, 1499, 1546, 1538, 1717, 2359, 2855, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{13}H_{20}N_2O_2$: 236.1525 (236.1520).

Tert-butyl ((5-cyclopropyl-1-(2-methoxyethyl)-1H-pyrrol-3-yl)methyl) carbamate

(5-7f)



To a solution of **5-6b** (74 mg, 0.2 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (20 mg, 0.1 mmol) and 2-methoxyethylamine (46 mg, 0.62 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 54 mg **5-7f** (yield: 94%) as a pale yellow oil.

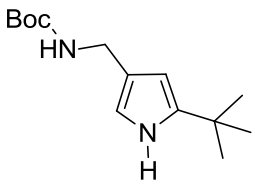
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.54 (s, 1H, NC*H*=), 5.71 (s, 1H, =C*H*-), 4.59 (br, 1H, N*H*Boc), 4.09 (m, 4H, NCH_2, CH_2NHBoc), 3.64 (t, 2H, J=5.9Hz, CH_2O), 3.34 (s, 3H, OCH_3), 1.65 (m, 1H, C*H*CH_2), 1.44 (s, 9H, Boc), 0.81 (m, 2H, CHCH_2), 0.57 (m, 2H, CHCH_2);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 135.6 (=*C*-), 119.4 (=*C*-), 118.8 (N*C*H=), 104.6 (*C*H), 78.9 (O*C*(CH_3)$_3$), 72.3 (*C*H_2O), 58.9 (O*C*H_3), 46.1 (N*C*H_2), 37.9 (*C*H_2NHBoc), 28.4 (OC(CH_3)$_3$), 6.7 (*C*HCH_2), 6 (CH*C*H_2);

IR (CCl_4): νmax 1046, 1122, 1172, 1238, 1366, 1390, 1495, 1547, 1717, 2360, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{26}N_2O_3$: 294.1943 (294.1947).

Tert-butyl ((5-(tert-butyl)-1H-pyrrol-3-yl)methyl)carbamate **5-7g**



To a solution of **5-6c** (134 mg, 0.36 mmol) in dioxane (2.5 ml) were added ammonium acetate (28 mg, 0.36 mmol) and aqua ammonia (20% NH_3) (88 mg, 1

mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 74 mg **5-7g** (yield: 82%) as a pale yellow oil.

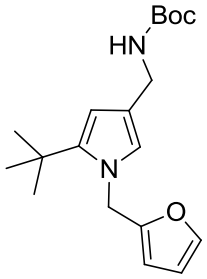
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.0 (br, 1H, N*H*), 6.57 (s, 1H, NC*H*=), 5.88 (s, 1H, C*H*), 4.66 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=4.6Hz, CH_2NHBoc), 1.45 (s, 9H, Boc), 1.27 (s, 9H, (CH_3)$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.7 (*C*O), 142.5 (=*Cq*NH), 120.4 (=*C*-), 114.2 (N*C*H=), 102.4 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 37.9 (*C*H$_2$NHBoc), 31.3 (*C*H(CH$_3$)$_3$), 30.4 (CH(*C*H$_3$)$_3$), 28.4 (OC(CH$_3$)$_3$);

IR (CCl_4): νmax 1047, 1081, 1172, 1230, 1311, 1366, 1466, 1493, 1581, 1716, 2855, 2928, 2961, 3408, 3461, 3489;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{24}N_2O_2$: 252.1838 (252.1845).

Tert-butyl-((5-(tert-butyl)-1-(furan-2-ylmethyl)-1H-pyrrol-3-yl)methyl) carbamate (5-7h)



To a solution of **5-6c** (82 mg, 0.22 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (22 mg, 0.12 mmol) and furfurylamine (44 mg, 0.44 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 66 mg **5-7h** (yield: 92%) as a pale red oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (m, 1H, O-C*H*=), 6.47 (s, 1H, NC*H*=), 6.32 (m, 1H, -C*H*=), 6.14 (d, 1H, J=2.5Hz, =C*H*-), 5.86 (s, 1H, C*H*), 5.13 (s, 2H,

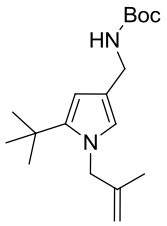
NC*H*$_2$), 4.60 (br, 1H, N*H*Boc), 4.09 (d, 2H, J=4.3Hz, C*H*$_2$NHBoc), 1.45 (s, 9H, Boc), 1.36 (s, 9H, (C*H*$_3$)$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 151.3, 142.4, 110.4, 104.9 (furan), 141.7 (=*C*-), 120.3 (N*C*H=), 120.3 (=*C*-), 108 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 44.9 (N*C*H$_2$), 37.9 (*C*H$_2$NHBoc), 31.9 (*C*H(CH$_3$)$_3$), 30.7 (CH(*C*H$_3$)$_3$), 28.4 (OC(*C*H$_3$)$_3$);

IR (CCl$_4$): νmax 1049, 1102, 1170, 1227, 1367, 1391, 1477, 1710, 2359, 2931, 2974, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{28}N_2O_3$: 332.2100 (332.2107).

Tert-butyl-((5-(tert-butyl)-1-(2-methylallyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7i)



To a solution of **5-6c** (74 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (18 mg, 0.1 mmol) and 2-methylallylamine (34 mg, 0.48 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 53 mg **5-7i** (yield: 88%) as a pale yellow oil.

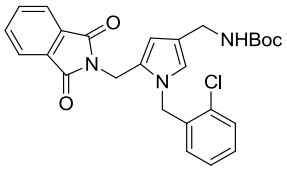
^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 6.43 (s, 1H, NC*H*=), 5.83 (s, 1H, C*H*), 4.89 (s, 1H, H*H*C=), 4.59 (br, 1H, N*H*Boc), 4.46 (m, 3H, *H*HC=, NC*H*$_2$), 4.10 (d, 2H, J=4.1Hz, C*H*$_2$NHBoc), 1.71 (s, 3H, C(C*H*$_3$)), 1.45 (s, 9H, Boc), 1.30 (s, 9H, (C*H*$_3$)$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 142.5 (=*C*-), 141.9 (*C*=CH$_2$), 120.8 (=*C*-), 118.6 (N*C*H=), 112.3 (C=*C*H$_2$), 104.5 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 53.9 (N*C*H$_2$), 38 (*C*H$_2$NHBoc), 31.9 (*C*H(CH$_3$)$_3$), 30.7 (CH(*C*H$_3$)$_3$), 28.5 (OC(*C*H$_3$)$_3$), 20 (C(*C*H$_3$));

IR (CCl$_4$: νmax 1024, 1172, 1242, 1366, 1467, 1495, 1545, 1539, 1717, 2855, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{30}N_2O_2$: 306.2307 (306.2307).

Tert-butyl-((1-(2-chlorobenzyl)-5-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrrol -3-yl)methyl)carbamate (5-7j)



To a solution of **5-5d** (47 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and (2-chlorophenyl)methanamine (28.2 mg, 0.2mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 39 mg **5-7j** (yield: 83 %) as a white solid (mp: 124-126 ℃).

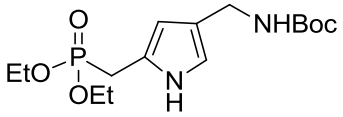
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.68 (m, 4H, PhthN), 7.23 (dd, 1H, J=1.2Hz, J=7.6Hz, Ar), 6.92 (m, 2H, Ar), 6.59 (s, 1H, NC*H*=), 6.39 (s, 1H, =C*H*-), 6.18 (d, 1H, J=6.4Hz, Ar), 5.31 (s, 2H, PhthNCH_2), 4.76 (s, 2H, NHCH_2Ar), 4.71 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=5.0Hz, CH_2NHBoc), 1.49 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 155.8 (*C*O), 133.8, 131.7, 129.1, 128.3, 127.4, 126.5, 123.1, 120.9 (Ar), 136.3 (Cq), 127 (Cq), 121 (=*C*H-), 111.3 (N*C*H=), 79.2 (O*C*(CH_3)$_3$), 48.6 (N*C*H_2Ph), 37.7 (*C*H_2NHBoc), 33.1 (NH*C*H_2Ar), 28.5 (OC(CH_3)$_3$);

IR (CCl_4): νmax 1027, 1050, 1085, 1112, 1171, 1219, 1346, 1366, 1390, 1425, 1415, 1469, 1447, 1718, 1771, 2929, 2979, 3063, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{26}H_{26}ClN_3O_4$: 479.1612 (479.1616).

Tert-butyl-((5-((diethoxyphosphoryl)methyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7k)



To a solution of **5-6e** (93 mg, 0.2 mmol) in dioxane (1 ml) were added ammonium acetate (15 mg, 0.2 mmol) and aqua ammonia (20% NH_3) (67 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 63 mg **5-7k** (yield: 92 %) as a pale yellow oil.

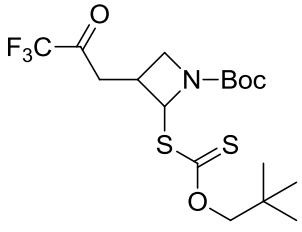
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.90 (br, 1H, N*H*), 6.59 (s, 1H, NC*H*=), 5.93 (s, 1H, =C*H*-), 4.66 (br, 1H, N*H*Boc), 4.10 (d, 2H, J=5.2Hz, CH_2NHBoc), 4.00 (m, 4H, 2OCH_2CH$_3$), 3.10 (d, 2H, J=20.2Hz, PCH_2), 1.42 (s, 9H, Boc), 1.23 (t, 6H, J=7.1Hz, 2OCH$_2$CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8(*C*O), 121.3 (=*C*-), 121.3, 121.2 (=*C*-), 116.1 (=*C*-), 108.1, 108 (N*C*H=), 79.1 (O*C*(CH$_3$)$_3$), 62.5, 62.4 (O*C*H$_2$CH$_3$), 37.8 (*C*H$_2$NHBoc), 28.5 (OC(*C*H$_3$)$_3$), 26.4, 24.9 (P*C*H$_2$), 16.4, 16.3 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1047, 1086, 1154, 1271, 1368, 1445, 1465, 1478, 1541, 1620, 1644, 1736, 1741, 2933, 2983, 3465;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{27}N_2O_5$: 346.1658 (346.1646).

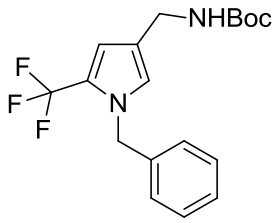
Tert-butyl-2-(((neopentyloxy)carbonothioyl)thio)-3-(3,3,3-trifluoro-2-oxopropyl) azetidine-1-carboxylate (5-6f)



Before doing the radical addition, we should add x mol **5-5f** in 6x ml cyclohexane and remove 4x ml cyclohexane. Then following the general procedure A for radical

addition, the reaction was carried out by adding **5-5f** (197 mg, 0.72 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (101 mg, 0.65 mmol) in cyclohexane (2 ml) and with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. In this case because of the hydrophilic property the mixture of four inseparate isomers were obtained and the solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl ((1-benzyl-5-(trifluoromethyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7l)



To a solution of **5-6f** (42.9 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and benzylamine (21 mg, 0.2 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 29 mg **5-7l** (yield step1+step2: 63 %) as a pale yellow oil.

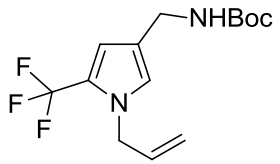
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.34 (m, 3H, Ar), 7.11 (d, 2H, J=7.4Hz, Ar), 6.64 (s, 1H, NC*H*=), 6.54 (s, 1H, =C*H*-), 5.11 (s, 2H, NCH_2), 4.67 (br, 1H, N*H*Boc), 4.11 (d, 2H, J=4.3Hz, CH_2NHBoc), 1.43 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 136.5, 128.7, 127.9, 127.1 (Ar), 123.9 (=*C*H-), 121.19 (q, 1H, J=266.8Hz, *C*F_3), 121.47 (q, 1H, J=37.3Hz, N*Cq*CF_3), 120.9 (*Cq*-CH_2NHBoc), 111.0 (=*C*H-), 79.3 (O*C*$(CH_3)_3$), 51.3 (N*C*H_2), 37.2 (*C*H_2NHBoc), 28.3 (OC$(CH_3)_3$);

IR (CCl_4): νmax 1040, 1110, 1163, 1269, 1367, 1459, 1498, 1547, 1543, 1551, 1720, 2856, 2928, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{21}F_3N_2O_2$: 354.1555 (354.1554).

Tert-butyl ((1-allyl-5-(trifluoromethyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7m)



To a solution of **5-6f** (85 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (19 mg, 0.1 mmol) and allyamine (46 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 55 mg **5-7m** (yield step1+step2: 68%) as a pale yellow oil.

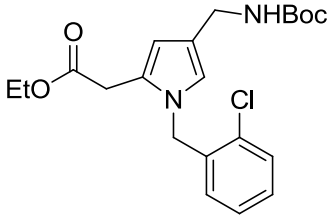
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.71 (s, 1H, NC*H*=), 6.49 (s, 1H, =C*H*-), 5.92 (m, 1H, C*H*=CH_2), 5.22 (d, 1H, J=10.2Hz, C*H*=CH*H*), 5.10 (d, 1H, J=16.9Hz, C*H*=C*H*H), 4.70 (br, 1H, N*H*Boc), 4.52 (d, 2H, J=5.7Hz, NCH_2), 4.11 (d, 2H, J=5.3Hz, CH_2NHBoc), 1.44 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 133.0 (*C*H=CH_2), 123.5 (=*C*H-), 121.1 (q, 1H, J=266.7Hz, *C*F_3), 120.9 (q, 1H, J=38.3Hz, N*Cq*CF_3), 120.6 (*Cq*-CH_2NHBoc), 118.1 (C*H*=CH_2), 110.9 (=*C*H-), 79.3 (O*C*(CH_3)$_3$), 50.2 (N*C*H_2), 37.1 (*C*H_2NHBoc), 28.3 (OC(CH_3)$_3$);

IR (CCl_4): νmax 1040, 1111, 1164, 1246, 1272, 1367, 1458, 1499, 1555, 1579, 1720, 2931, 2979, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{19}F_3N_2O_2$: 304.1399 (304.1411).

Ethyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-1-(2-chlorobenzyl)-1H- pyrrol--2-yl) acetate (5-7o)



To a solution of **5-6g** (40 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene

sulfonic acid monohydrate (19 mg, 0.1 mmol) and (2-chlorophenyl)methanamine (28.2 mg, 0.2mmol). The reaction mixture was heated at 80 ℃ under nitrogen for 1 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 25 mg **5-7o** (yield: 64 %) as a yellow oil and 6 mg **5-7p** (yield: 18 %) as a pale yellow oil.

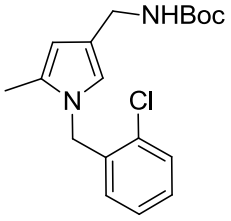
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.36 (m, 1H, Ar), 7.18 (m, 2H, Ar), 6.56 (s, 1H, NC*H*=), 6.49 (d, 1H, J=7.3Hz, Ar), 6.09 (s, 1H, =C*H*-), 5.11 (s, 2H, NCH_2Ph), 4.67 (br, 1H, N*H*Boc), 4.14 (d, 2H, J=5.0Hz, CH_2NHBoc), 4.02 (q, 2H, J=7.1Hz, OC$H_2$$CH_3$), 3.45 (s, 2H, CH_2COOEt), 1.44 (s, 9H, Boc), 1.19 (t, 3H, J=7.2Hz, OCH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.2 (*CO*OEt), 155.7 (*C*O), 135.6, 131.9, 129.2, 128.7, 127.5, 127.2 (Ar), 125.5 (N*Cq*=), 120.6 (N*C*H=), 120.4 (*Cq*CH_2NHBoc), 109.2 (=*C*H-), 79.0 (O*C*(CH_3)$_3$), 61.0 (O*C*$H_2$$CH_3$), 48.2 (N*C*$H_2$), 37.7 (*C*$H_2$NHBoc), 32.5 (*C*$H_2$COOEt), 28.4 (OC(*C*$H_3$)$_3$), 14.0 ($OCH_2$*C*$H_3$);

IR (CCl_4): νmax 1040, 1050, 1170, 1243, 1263, 1367, 1446, 1497, 1547, 1574, 1615, 1655, 1719, 2930, 2980, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{27}ClN_2O_4$: 406.1659 (406.1656).

5-7p tert-butyl ((1-(2-chlorobenzyl)-5-methyl-1H-pyrrol-3-yl)methyl)carbamate



^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.36 (m, 1H, Ar), 7.19 (m, 2H, Ar), 6.52 (s, 1H, NC*H*=), 6.46 (d, 1H, J=7.2Hz, Ar), 5.92 (s, 1H, =C*H*-), 5.02 (s, 2H, NCH_2Ph), 4.64 (br, 1H, N*H*Boc), 4.14 (d, 2H, J=5.0Hz, CH_2NHBoc), 2.09 (s, 3H, CH_3), 1.45 (s, 9H, Boc);

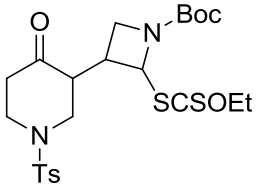
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 135.9, 131.8, 129.4, 129.2, 128.5, 127.5 (Ar), 127.3 (N*Cq*=), 120.38 (N*C*H=), 118.995 (*Cq*CH_2NHBoc), 107.1 (=*C*H-),

79.0 (O*C*(CH_3)$_3$), 47.9 (N*C*H_2), 37.8 (*C*H_2NHBoc), 28.4 (OC(*C*H_3)$_3$), 11.7 (*C*H_3);

IR (CCl_4): νmax 1050, 1172, 1239, 1367, 1390, 1446, 1497, 1614, 1718, 2856, 2929, 2979, 3410, 3461;

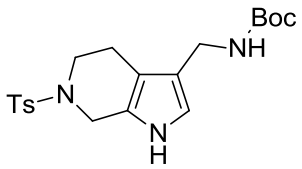
HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{23}ClN_2O_2$: 334.1448 (334.1656).

Tert-butyl-2-((ethoxycarbonothioyl)thio)-3-(4-oxo-1-tosylpiperidin-3-yl)azetidine - -1-carboxylate (5-10a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9a** (300 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (137 mg, 0.88 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl ((6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridin-3-yl)methyl) carbamate (5-11a)



To a solution of **5-10a** (67 mg, 0.13 mmol) in dioxane (0.7 ml) were added ammonium acetate (10 mg, 0.13 mmol) and aqua ammonia (20% NH_3) (41 mg, 0.51 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 48 mg **5-11a** (yield step1+step2: 67 %) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.84 (br, 1H, N*H*) ppm 7.70 (d, 2H, J=8.2Hz,

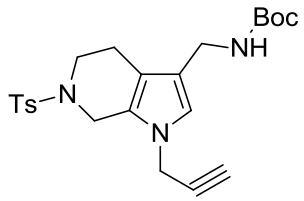
Ar), 7.30 (d, 2H, J=8.0Hz, Ar), 6.52 (s, 1H, NC*H*=), 4.55 (br, 1H, N*H*Boc), 4.11 (m, 4H, CH_2NTs, CH_2NHBoc), 3.38 (t, 2H, J=5.7Hz, CH_2NTs), 2.70 (t, 2H, J=5.4Hz, CH_2CH$_2$NTs), 2.41 (s, 3H, ArCH_3), 1.46 (s, 9H, Boc);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.7 (*C*O), 143.4, 129.7, 127.612, 124.6 (Ar), 134.1 (=*C*-Ph), 117.3 (=*C*-), 115.6 (N*C*H=), 111.9 (*C*H), 79.3 (O*C*(CH$_3$)$_3$), 43.6 (*C*H$_2$NTs), 43.2 (*C*H$_2$NTs), 36.2 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 23.4 (Ar*C*H$_3$), 21.5 (*C*H$_2$CH$_2$NTs);

IR (CCl$_4$): νmax 1169, 1239, 1359, 1465, 1496, 1624, 1711, 1740, 2855, 2927, 3483;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{27}N_3O_4S$: 405.1722 (405.1723).

Tert-butyl-((1-(prop-2-yn-1-yl)-6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c] pyridin-3-yl)methyl)carbamate (5-11b)



To a solution of **5-10a** (66 mg, 0.13 mmol) in dioxane (0.7 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and mono-propargylamine (21 mg, 0.38 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 50 mg **5-11b** (yield step1+step2: 66 %) as a yellow solid (mp: 102-103 ℃).

^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 7.69 (d, 2H, J=8.1Hz, Ar), 7.29 (d, 2H, J=8.0Hz, Ar), 6.53 (s, 1H, NC*H*=), 4.54 (br, 1H, N*H*Boc), 4.42 (d, 2H, J=2.2Hz, NCH_2), 4.04 (m, 4H, CH_2NTs, CH_2NHBoc), 3.40 (t, 2H, J=5.6Hz, CH_2NTs), 2.70 (t, 2H, J=5.4Hz, CH_2CH$_2$NTs), 2.40 (s, 3H, ArCH_3), 2.34 (s, 1H, CC*H*), 1.45 (s, 9H, Boc);

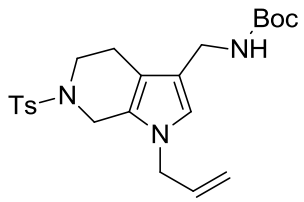
^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.6 (*C*O), 143.4, 129.5, 127.5, 125.3 (Ar), 133.9 (=*C*-Ph), 118.5 (=*C*-), 116.9 (N*C*H=), 112.9 (*C*H), 79.2 (O*C*(CH$_3$)$_3$), 77.8 (CH$_2$*C*CH$_2$), 73.4 (C*C*H$_2$), 43.5 (*C*H$_2$NTs), 43.1 (*C*H$_2$NTs), 36 (*C*H$_2$NHBoc), 35.7

(N*C*H_2), 28.4 (OC(CH_3)$_3$), 22.2 (Ar*C*H_3), 21.4 (*C*$H_2$$CH_2$NTs);

IR (CCl_4): νmax 1022, 1100, 1168, 1361, 1458, 1653, 1762, 2361, 2855, 2927, 3675, 3712;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{29}N_3O_4S$: 443.1879 (443.1885).

Tert-butyl-((1-allyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridin-3-yl) methyl)carbamate (5-11c)



To a solution of **5-10a** (67 mg, 0.13 mmol) in dioxane (0.7 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and allylamine (21mg, 0.37 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 48 mg **5-11c** (yield step1+step2: 63%) as a light yellow solid (mp: 112-113 ℃).

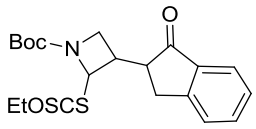
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.69 (d, 2H, J=8.1Hz, Ar), 7.28 (d, 2H, J=8.0Hz, Ar), 6.41 (s, 1H, NC*H*=), 5.79 (m, 1H, -C*H*=), 5.09 (d, 1H, J=10.2Hz, -CH=CH*H*), 4.83 (d, 1H, J=17.1Hz, -CH=C*H*H), 4.52 (br, 1H, N*H*Boc), 4.25 (d, 2H, J=5.0Hz, NC*H*$_2$), 4.08 (s, 2H, C*H*$_2$NTs), 4.04 (d, 2H, J=5.1Hz, C*H*$_2$NHBoc), 3.38 (t, 2H, J=5.7Hz, C*H*$_2$NTs), 2.59 (t, 2H, J=5.4Hz, C*H*$_2$$CH_2$NTs), 2.40 (s, 3H, ArC*H*$_3$), 1.45 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.6 (*C*O), 143.3, 129.5, 127.5, 125.3 (Ar), 134.1 (=*C*-Ph), 133.8 (-*C*H=CH_2), 118.7 (=*C*-), 116.8 (CH=*C*H_2), 116.2 (N*C*H=), 112.1 (*C*H), 79.2 (O*C*(CH_3)$_3$), 48.7 (N*C*H_2), 43.6 (*C*H_2NTs), 43.2 (*C*H_2NTs), 36.1 (*C*H_2NHBoc), 28.4 (OC(CH_3)$_3$), 22.2 (Ar*C*H_3), 21.4 (*C*$H_2$$CH_2$NTs);

IR (CCl_4): νmax 1021, 1100, 1237, 1305, 1357, 1366, 1466, 1497, 1534, 1547, 1716, 2855, 2927, 3459;

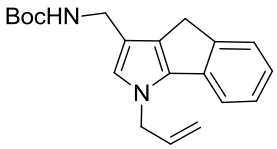
HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{31}N_3O_4S$: 445.2035 (445.2033).

Tert-butyl-2-((ethoxycarbonothioyl)thio)-3-(1-oxo-2,3-dihydro-1H-inden-2-yl) azetidine-1-carboxylate (5-10b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9b** (200 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (137 mg, 0.88 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl-((1-allyl-1,4-dihydroindeno[1,2-b]pyrrol-3-yl)methyl)carbamate (5-11d)



To a solution of **5-10b** (100 mg, 0.25 mmol) in dioxane (1.2 ml) were added *p*-toluene sulfonic acid monohydrate (23 mg, 0.12 mmol) and allylamine (57 mg, 1 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 74 mg **5-11d** (yield step1+step2: 68%) as a yellow solid (mp: 132-133 ℃).

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.43 (d, 1H, J=7.4Hz, Ar), 7.30 (d, 1H, J=7.5Hz, Ar), 7.24 (m, 1H, Ar), 7.08 (m, 1H, Ar), 6.61 (s, 1H, NC*H*=), 6.05 (m, 1H, C*H*=CH_2), 5.22 (dd, 1H, J=1.3Hz, J=14.1Hz, C*H*H=CH), 5.12 (dd, 1H, J=1.1Hz, J=17.1Hz, CH*H*=CH), 4.72 (br, 1H, N*H*Boc), 4.71 (d, 2H, J=5.2Hz，NCH_2CH=), 4.25 (d, 2H, J=5.4Hz, CH_2NHBoc), 3.48 (s, 2H, CH_2Ar), 1.49 (s, 9H, Boc);

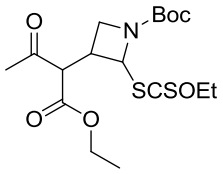
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 146.9 (NCq) 133.9 (*C*H=CH_2),

138.1, 135.3, 126.2, 125.4, 116.4 (Ar), 127.9 (CH_2NHBocC*q*), 122.9 (N*C*H=), 117.1 (CH=*C*H_2), 116.6 (C*q*), 79.1 (O*C*(CH_3)$_3$), 50.5 (N*C*H_2), 37 (*C*H_2NHBoc), 29.9 (*C*H_2Ar), 28.4 (OC(*C*H_3)$_3$);

IR (CCl_4): νmax 1040, 1050, 1086, 1133, 1173, 1227, 1252, 1295, 1365, 1432, 1446, 1494, 1526, 1547, 1712, 2855, 2928, 2979, 3068, 3456;

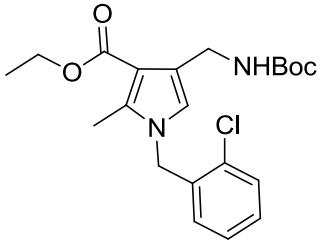
HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{24}N_2O_2$: 324.1838 (324.1836).

Tert-butyl-3-(1-ethoxy-1,3-dioxobutan-2-yl)-2-((ethoxycarbonothioyl)thio)--azetidine-1-carboxylate (5-10c)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9c** (100 mg, 0.4 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (68 mg, 0.45 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was without further purification.

Ethyl-4-(((tert-butoxycarbonyl)amino)methyl)-1-(2-chlorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (5-11e)



To a solution of **5-10c** (45 mg, 0.11 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9mg, 0.05 mmol) and (2-chlorophenyl) methanamine (31mg, 0.22 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v)

to afforded 39 mg **5-11e** (yield step1+step2: 61 %) as a pale yellow oil.

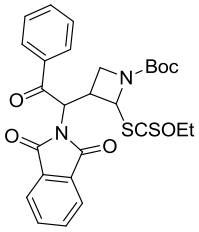
^{1}H NMR (400 MHz; $CDCl_3$): 7.38 (d, 1H, J=7.8Hz, Ar), 7.18 (m, 2H, Ar), 6.54 (s, 1H, NC*H*=), 6.49 (d, 1H, J=6.8Hz, Ar), 5.45 (br, 1H, N*H*Boc), 5.05 (s, 2H, NCH_2Ph), 4.29 (m, 4H, CH_2NHBoc, COOCH_2), 2.37 (s, 3H, CH_3), 1.41 (s, 9H, Boc), 1.36 (t, 3H, J=7.1Hz, $COOCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 155.9 (*C*O), 137, 132.1, 129.5, 129, 127.5, 127.4 (Ar), 134.5, 122.7, 110.9 (Cq), 120.6 (N*C*H=), 78.8 (O*C*$(CH_3)_3$), 59.7 ($COOCH_2$), 48.1 (NCH_2Ph), 37.1 (CH_2NHBoc), 28.5 (OC$(CH_3)_3$), 14.5 ($COOCH_2CH_3$), 11.5 (CH_3);

IR (CCl_4): νmax 1012, 1045, 1170, 1245, 1366, 1391, 1449, 1498, 1718, 2928, 2979, 2979, 3459;

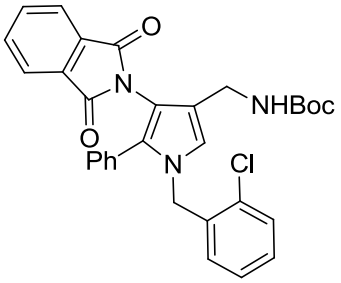
HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{27}ClN_2O_4$: 406.1659 (406.1652).

Tert-butyl-3-(1-(1,3-dioxoisoindolin-2-yl)-2-oxo-2-phenylethyl)-2-((ethoxycarbono thioyl)thio) azetidine-1-carboxylate (5-10d)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9d**(120 mg, 0.32 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (56 mg, 0.34 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do the step without further purification.

Tert-butyl((1-(2-chlorobenzyl)-4-(1,3-dioxoisoindolin-2-yl)-5-phenyl-1H-pyrrol-3-yl) methyl) carbamate (5-11f)



To a solution of **5-10d** (38 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and (2-chlorophenyl)methanamine (28 mg, 0.2 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 43 mg **5-11f** (yield step1+step2: 58%) as a pale yellow oil.

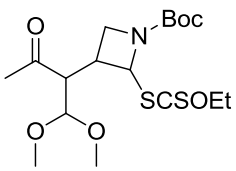
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.83 (m, 2H, PhthN), 7.70 (m, 2H,PhthN), 7.33 (m, 1H, Ar), 7.23 (m, 7H, Ar), 6.83 (m, 1H, Ar), 6.77 (s, 1H, NC*H*=), 5.08 (s, 2H, NCH_2), 4.83 (br, 1H, N*H*Boc), 4.09 (d, 2H, J=5.5Hz, NCH_2), 1.30 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 168.3, 155.5 (*C*O), 135.3, 133.9, 132.9, 132.1, 131.9, 129.7, 129.5, 129.3, 128.9, 128.6, 128.3, 128.3, 123.5 (Ar), 127.4 (*Cq*NthPh),119.9 (N*C*H=), 119.3 (*Cq*CH_2NHBoc), 111.5 (=*C*(Ph)N), 78.9 (O*C*$(CH_3)_3$), 48.7 (N*C*H_2), 35 (*C*H_2NHBoc), 28.2 (OC(*C*$H_3)_3$);

IR (CCl_4): νmax 1041, 1085, 1114, 1171, 1247, 1366, 1391, 1446, 1499, 1725, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{31}H_{28}ClN_3O_4$: 541.1768 (541.1773).

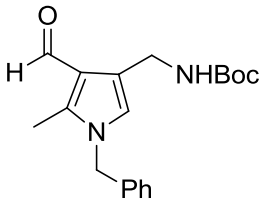
Tert-butyl-3-(1,1-dimethoxy-3-oxobutan-2-yl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-10e)



Following the general procedure A for radical addition, the reaction was carried out

with a solution of **5-9e** (100 mg, 0.4 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (67 mg, 0.44 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do the next step without further purification.

Tert-butyl-((1-benzyl-4-formyl-5-methyl-1H-pyrrol-3-yl)methyl)carbamate (5-11g)



To a solution of **5-10e** (119 mg, 0.29 mmol) in dioxane (1.5 ml) were added *p*-toluene sulfonic acid monohydrate (28 mg, 0.15 mmol) and benzylamine (64 mg, 0.6 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 80 mg **5-11g** (yield step1+step2: 62%) as a pale red oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 9.87 (s, 1H, C*H*O), 7.31 (m, 3H, Ar), 7.01 (d, 2H, J=6.7Hz, Ar), 6.59 (s, 1H, NC*H*=), 5.79 (br, 1H, N*H*Boc), 4.98 (s, 2H, NCH_2Ph), 4.25 (d, 2H, J=6.3Hz, CH_2NHBoc), 2.37 (s, 3H, CqCH_3), 1.40 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 185.4 (*C*HO), 155.9 (*C*O), 140.6 (*C*qCH_3), 135.9, 128.9, 127.9, 126.4 (Ar), 121.5 (*C*qCHO), 121.5 (NC*H*=), 120.7 (*C*qCH_2NHBoc), 78.7 (O*C*$(CH_3)_3$), 50.2 (N*C*H_2Ph), 36.2 (*C*H_2NHBoc), 28.4 (OC(*C*$H_3)_3$), 9.8 (Cq*C*H_3);

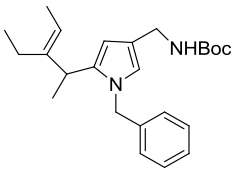
IR (CCl_4): νmax 1017, 1077, 1046, 1118, 1172, 1245, 1284, 1366, 1454, 1466, 1497, 1661, 1712, 2855, 2928, 2979, 3439;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{24}N_2O_3$: 328.1787 (328.1788).

Tert-butyl-3-(2,2-diethyl-3-methyl-4-oxocyclobutyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-16)

Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-15** (260 mg, 1 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (170 mg, 1.1 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

(*E*)-Tert-butyl-((1-benzyl-5-(3-ethylpent-3-en-2-yl)-1H-pyrrol-3-yl)methyl) carbamate (5-17a)



To a solution of **5-16** (45 mg, 0.11 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and benzylamine (24 mg, 0.22 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 28 mg **5-17a** (yield step1+step2: 48 %) as a pink oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.28 (m, 3H, Ar), 6.95 (d, 2H, J=7.2Hz, Ar), 6.48 (s, 1H, NC*H*=), 5.96 (s, 1H, =C*H*-), 5.09 (q, 1H, J=6.8Hz, CH_3C*H*=), 4.92 (m, 2H, NCH_2), 4.62 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=3.9Hz, CH_2NHBoc), 3.22 (q, 1H, J=7.1Hz, C*H*CH_3), 1.94 (q, 2H, J=7.5Hz, C$H_2$$CH_3$), 1.54 (d, 3H, J=6.8Hz, CH_3CH=), 1.46 (s, 9H, Boc), 1.27 (d, 3H, J=7.1Hz, CHCH_3), 0.77 (t, 3H, J=7.5Hz, CH_2CH_3);

Diastereoisomer 2: δ_H ppm 7.28 (m, 3H, Ar), 6.95 (d, 2H, J=7.2Hz, Ar), 6.48 (s, 1H, NC*H*=), 5.98 (s, 1H, =C*H*-), 5.20 (q, 1H, J=6.5Hz, CH_3C*H*=),4.92 (m, 2H, NCH_2),

4.62 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=3.9Hz, CH_2NHBoc), 3.76 (q, 1H, J=7.6Hz, C*H*CH_3), 1.94 (q, 2H, J=7.5Hz, CH_2CH_3), 1.57 (d, 3H, J=6.0Hz, CH_3CH=), 1.46 (s, 9H, Boc), 1.27 (d, 3H, J=7.1Hz, CHCH_3), 0.77 (t, 3H, J=7.5Hz, CH_2CH_3);

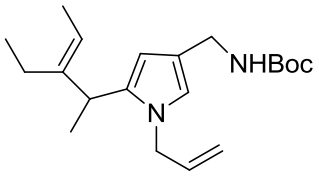
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 155.8 (*C*O), 144.77 (CH_2*Cq*=CH), 138.5, 128.6, 127.1, 126.44 (Ar), 136.59 (=*Cq*N), 119.34 (=*C*H-) 119.1 (CH_3*C*H=), 116.9 (=*Cq*-CH_2NBoc), 106.2 (=*C*H-), 79 (O*C*$(CH_3)_3$), 49.8 (NCH_2), 38.6 (*C*H_2NHBoc), 38.1 (*C*HCH_3), 29.6 (OC(*C*$H_3)_3$), 21.3 (*C*H_2CH_3), 19.6 (CH*C*H_3), 13.4 (*C*H_3CH=), 13.1 (CH_2*C*H_3);

Diastereoisomer 2: δ_C ppm 155.8 (*C*O), 144.71 (CH_2*Cq*=CH), 138.4, 128.5, 127.1, 126.40 (Ar), 136.54 (=*Cq*N), 119.32 (=*C*H-), 119.1 (CH_3*C*H=), 116.9 (=*Cq*-CH_2NBoc), 106.1 (=*C*H-), 78.9 (O*C*$(CH_3)_3$), 49.7 (NCH_2), 38.0 (*C*H_2NHBoc), 32.1 (*C*HCH_3), 28.4 (OC(*C*$H_3)_3$), 24.2 (*C*H_2CH_3), 18.1 (CH*C*H_3), 12.7 (*C*H_3CH=), 12.6 (CH_2*C*H_3);

IR (CCl_4): νmax 1173, 1246, 1339, 1366, 1392, 1455, 1497, 1539, 1718, 2875, 2932, 2968, 3409, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{24}H_{34}N_2O_2$: 382.2620 (382.2614).

(*E*)-Tert-butyl-((1-allyl-5-(3-ethylpent-3-en-2-yl)-1H-pyrrol-3-yl)methyl)carbamate (5-17b)



To a solution of **5-16** (82 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (19 mg, 0.1 mmol) and allyamine (46 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 52 mg **5-17b** (yield step1+step2: 56%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 6.46 (s, 1H, NC*H*=), 5.91 (s, 1H, =C*H*-), 5.84 (m, 1H, NCH_2CH), 5.10 (m, 2H, CH=CH_2), 4.95 (m, 1H, CH_3CH=), 4.61 (br, 1H, N*H*Boc), 4.31 (m, 2H, NCH_2), 4.13 (d, 2H, J=4.3Hz, CH_2NHBoc), 3.33 (q, 1H, J=6.9Hz, C*H*CH_3), 1.98 (q, 2H, J=7.5Hz, CH_2CH_3), 1.57 (d, 3H, J=6.8Hz, CH_3CH=), 1.45 (s, 9H, Boc), 1.31 (d, 3H, J=7.1Hz, CHCH_3), 0.80 (t, 3H, J=7.4Hz, CH_2CH_3);

Diastereoisomer 2: δ_H ppm 6.46 (s, 1H, NC*H*=), 5.91 (s, 1H, =C*H*-), 5.84 (m, 1H, NCH_2CH), 5.10 (m, 2H, CH=CH_2), 4.95 (m, 1H, CH_3CH=), 4.61 (br, 1H, N*H*Boc), 4.31 (m, 2H, NCH_2), 4.13 (d, 2H, J=4.3Hz, CH_2NHBoc), 3.87 (q, 1H, J=7.1Hz, C*H*CH_3), 1.98 (q, 2H, J=7.5Hz, CH_2CH_3), 1.70 (d, 3H, J=6.8Hz, CH_3CH=), 1.45 (s, 9H, Boc), 1.31 (d, 3H, J=7.1Hz, CHCH_3), 0.80 (t, 3H, J=7.4Hz, CH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 155.7 (*C*O), 144.8 (CH_2*Cq*=CH), 136.04 (=*Cq*N), 134.5 (NCH_2*C*H), 119.3 (=*Cq*-CH_2NBoc), 119.0 (=*C*H-), 116.5 (CH=*C*H_2), 116.3 (CH_3*C*H=), 105.70 (=*C*H-), 79.0 (O*C*$(CH_3)_3$), 48.6 (N*C*H_2), 38.4 (*C*HCH_3), 38.0 (*C*H_2NHBoc), 28.4 (OC(*C*$H_3)_3$), 21.3 (*C*H_2CH_3), 19.5 (CH*C*H_3), 13.3 (*C*H_3CH=), 13.1 (CH_2*C*H_3);

Diastereoisomer 2: δ_C ppm 155.7 (*C*O), 144.02 (CH_2*Cq*=CH), 136.2 (=*Cq*N), 134.7 (NCH_2*C*H), 119.2 (=*Cq*-CH_2NBoc), 119.0 (=*C*H-), 118.5 (CH_3*C*H=), 116.6 (CH=*C*H_2), 105.77 (=*C*H-), 78.9 (O*C*$(CH_3)_3$), 48.4 (NCH_2), 38.0 (*C*H_2NHBoc), 31.9 (*C*HCH_3), 28.4 (OC(*C*$H_3)_3$), 24.1 (*C*H_2CH_3), 18.0 (CH*C*H_3), 12.7 (*C*H_3CH=), 12.6 (CH_2*C*H_3);

IR (CCl_4): νmax 992, 1025, 1046, 1123, 1171, 1246, 1366, 1390, 1467, 1494, 1539, 1717, 2874, 2858, 2929, 2966, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{32}N_2O_2$: 332.2464 (332.2458).